7. Summary of Safety

# 7. SUMMARY OF SAFETY

## 7.1. Introduction

Safety information from 25 studies (Table 1) of FluMist in children, adolescents, and adults are presented. Among the 25 studies, 21 are complete, three have completed enrollment and follow-up with ongoing analyses [VA CSP #448, Study AV012 (Year Three) and Study AV019] and one is ongoing with enrollment in progress (Study AV018). Twenty-two studies were conducted by Aviron, two studies were conducted by Wyeth-Lederle vaccines (Wyeth), two by the National Institutes of Health (NIH) and one by the Veterans Administration Cooperative Studies Program (study of patients with chronic obstructive pulmonary disease).

Available data from these studies of FluMist are summarized herein including estimated enrollment from Studies AV012 year three and AV019. Enrollment in ongoing Study AV018 is not included in this report, however, serious adverse events reported from Study AV018 and from all FluMist studies as of June 1, 2001 are presented.

These clinical studies demonstrated that FluMist is safe and well-tolerated.

### 7.1.1. Methods

Safety data in this document include reactogenicity events, other non-serious adverse events, medically attended events, and serious adverse events. Serious adverse events (SAEs) were collected in all studies. Reactogenicity events (REs) and other non-serious adverse events (AEs) were collected in all studies except Study AV012 (the four-year open-label safety trial conducted in collaboration with the NIH in Temple, Texas by investigators at the Baylor College of Medicine) and Study AV019 (the placebo-controlled safety trial conducted in Northern California by investigators at Kaiser Permanente Medical Care Program). In Study AV019, in addition to SAEs, medically attended events (MAEs), as captured in the HMO database, were collected for analyses of safety.

Reactogenicity events (REs) are pre-specified adverse events systematically recorded on diary cards (a grid of check boxes for each event and each day) during the immediate post-vaccination period either by the parent/guardian of child participants or by adult participants. In general, REs were recorded for 10 days in children and for seven days in adults. The selection of the events to be collected systematically was based on events expected to occur with wild-type influenza infection. The events included fever, runny nose or nasal congestion, cough, sore throat, irritability, muscle aches, headache, chills, vomiting and decreased activity. In

addition to rates of REs, additional analyses were performed by combining REs into event complexes that might be considered influenza-like illness (ILI). These complexes include: any three or more events on the same day; the Centers for Disease Control and Prevention Influenza-Like Illness (CDC-ILI) definition (temperature ≥100°F oral with cough or sore throat on the same day or consecutive days); and the event complex of temperature ≥100°F oral with cough and runny nose/nasal congestion on the same day).

Adverse events (AEs), other than REs, were defined as any unfavorable and unintended change in the structure, function, or chemistry of the body, or worsening of a pre-existing condition temporally associated with the use of the study product. The investigators determined the relationship of each AE to study treatment. AEs were collected on diary cards within the same time periods as reactogenicity data (7 to 10 days) and were transcribed to an adverse event Case Report Form (CRF). In this report, adverse events occurring with a frequency of ≥1% for participants in any treatment group are presented by body system and preferred term.

An SAE is defined as an AE that is fatal, immediately life-threatening, results in permanent or significant disability, results in or prolongs an existing in-patient hospitalization, is a congenital anomaly/birth defect, or is an important medical event that may jeopardize the participant and may require medical or surgical intervention to prevent one of the preceding outcomes. An SAE may have a number of presenting signs and/or symptoms, but one of these will be the primary basis on which the event is classified as an SAE. The reporting investigator determines the relationship between vaccination and an SAE using the following definitions:

a) Definitely not: No relationship. The study vaccine did not cause the event.

b) Probably not: Relationship is not likely. Although it is unlikely that the study vaccine caused this event, causality can not be entirely ruled out.

c) Possibly: Relationship may exist. There is at least a reasonable possibility that the event was caused by the study vaccine, although the likelihood is low.

d) Probably: Relationship is likely. It is likely that the study vaccine caused the event.

e) Definitely: Unquestionable relationship. The event was directly attributable to the study vaccine.

In general, the reporting period for SAEs was 28 days following vaccination of adults and 42 days following vaccination of children and adolescents. SAEs considered to be related to vaccine were reported for the duration of the studies. Events where causal relationship was not

assessed or was not known were noted as unknown and considered vaccine-related. In general, study staff contacted participants or the parents/guardians at designated times and/or at the end of the study to inquire about SAEs. Adult participants or parents/guardians of participants were asked to notify study staff immediately if any unexpected events or SAEs occurred. Study staff were required to report all SAEs within 24 hours of awareness of the event to the sponsor.

### 7.2. Participant Exposure

A total of 24,957 participants have received FluMist in the trials summarized in this report. Table 47 presents the total number of doses of FluMist and placebo administered in these trials by population and age groups. Among the 24,957 participants who have received FluMist in these trials, 12,069 were healthy children 1–8 years of age, 6,321 were healthy children or adolescents 9–17 years of age, and 3,947 were healthy adults 18–64 years of age (Table 47).

In addition to the healthy populations noted above, a total of 2,620 participants at high-risk for influenza morbidity based on age or underlying conditions have received FluMist. This includes 23 HIV-infected children, 28 HIV-infected adults, 1,331 children or adults with asthma (754 children 1–8 years of age, 540 children or adolescents 9–17 years of age, and 37 adults 18–64 years of age), and 1,238 adults (131 ≥65 years of age and 1,107 adults with COPD) (Table 47).

**Table 47**
**Total Number of Doses of FluMist and Placebo Administered in FluMist Trials in Healthy and High-Risk Populations**

| Population | Doses of FluMist | | | | | | Doses of Placebo Total |
|---|---|---|---|---|---|---|---|
| | First | Second | Third | Fourth | Fifth | Total | |
| Healthy Children | | | | | | | |
| 1–8 years | 12069 | 6698 | 1584 | 677 | 469 | 21499[a] | 4860 |
| Healthy Children and Adolescents | | | | | | | |
| 9–17 years | 6321 | 1564 | 673 | | 10 | 8568 | 1370 |
| Healthy Adults | | | | | | | |
| 18–64 years | 3947 | 104 | 16 | | | 4067 | 1662 |
| Total Healthy Populations | 22337 | 8366 | 2273 | 677 | 479 | 34134[a] | 7892 |
| | | | | | | | |
| HIV-infected | | | | | | | |
| 1–8 years | 23 | 16 | | | | 39 | 24 |
| 18–64 years | 28 | | | | | 28 | 29 |
| Subtotal | 51 | 16 | | | | 67 | 53 |
| Asthmatics | | | | | | | |
| 1–8 years | 754 | 281 | 45 | | | 1080 | 0 |
| 9–17 years | 540 | 232 | 64 | | | 836 | 24 |
| 18–64 years | 37 | 5 | 1 | | | 43 | 13 |
| Subtotal | 1331 | 518 | 110 | | | 1959 | 37 |
| Adults ≥65 years | 131 | | | | | 131 | 101 |
| Adults ≥50 years with COPD | 1107 | | | | | 1107 | 1108 |
| Total High-Risk Populations | 2620 | 534 | 110 | | | 3264 | 1299 |
| | | | | | | | |
| Total All Studies | 24957 | 8900 | 2383 | 677 | 479 | 37398[a] | 9191 |

[a] Includes two participants who received a sixth dose.

## 7.3. Overview of FluMist Safety

FluMist was safe and well-tolerated when administered to healthy participants according to the following schedules:

- Children 1–8 years: one- or two-dose primary vaccination followed by one dose re-vaccination annually
- Children and adolescents 9–17 years: one dose annually
- Adults 18–64 years: one dose annually

FluMist was safe and well-tolerated when evaluated in limited numbers of participants in the following high-risk populations:

- Children, adolescents, and adults with asthma
- HIV-infected children
- HIV-infected adults
- Adults with chronic obstructive pulmonary disease [administered concurrently with Trivalent Inactivated Influenza vaccine (TIV)]

Recent data from a trial of FluMist in young children in daycare demonstrated a low rate of transmission.

### 7.3.1. Overall Demographic Characteristics

The demographic characteristics of healthy children, adolescents and adults, by age group, are presented in Table 48. Approximately half of the FluMist and placebo recipients were female.

The racial/ethnic distribution was fairly well balanced between FluMist and placebo recipients within each age group (1–8, 9–17, 18–64); however, compared to adults more children were of Hispanic origin and more adults were white (Table 48).

The demographic characteristics of children, adolescents, and adults at high-risk for influenza morbidity are presented in Table 49. Most elderly adults and nearly all adults with COPD were male. More adults with COPD were white. In the other groups at high-risk, more females and race/ethnicities other than white were represented.

## Table 48
## Demographic Characteristics of All Healthy Participants at Time of Initial Vaccination with FluMist or Placebo

| Characteristics | Overall 1–64 Years | | Children (1–8 Years) | | Children & Adolescents (9–17 Years) | | Adults (18–64 Years) | |
|---|---|---|---|---|---|---|---|---|
| | FluMist 22261 | Placebo 5797 | FluMist 11993 | Placebo 2792 | FluMist 6321 | Placebo 1359 | FluMist 3947 | Placebo 1646 |
| **Age (years)** | | | | | | | | |
| Median | 8.0 | 9.0 | 4.0 | 4.0 | 12.0 | 12.0 | 36.0 | 37.0 |
| Mean | 12.1 | 15.2 | 4.0 | 3.9 | 12.0 | 12.1 | 36.6 | 37.0 |
| Range | 1–64 | 1–64 | 1–8 | 1–8 | 9–17 | 9–17 | 18–64 | 18–64 |
| 25th percentile | 3 | 4 | 2 | 2 | 10 | 10 | 28 | 29 |
| 75th percentile | 14 | 25 | 6 | 5 | 14 | 14 | 45 | 44 |
| **Gender, %** | | | | | | | | |
| Male | 10780 (48.4) | 2810 (48.5) | 5912 (49.3) | 1376 (49.3) | 3101 (49.1) | 680 (50.0) | 1767 (44.8) | 754 (45.8) |
| Female | 11476 (51.6) | 2987 (51.5) | 6081 (50.7) | 1416 (50.7) | 3215 (50.9) | 679 (50.0) | 2180 (55.2) | 892 (54.2) |
| Not Reported | 5 ( 0.1) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 5 ( 0.1) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| **Race/Ethnicity, %** | | | | | | | | |
| White | 14762 (66.3) | 3844 (66.3) | 7440 (62.0) | 1674 (60.0) | 4093 (64.8) | 804 (59.2) | 3229 (81.8) | 1366 (83.0) |
| Black | 2001 ( 9.0) | 480 ( 8.3) | 1156 ( 9.6) | 198 ( 7.1) | 478 ( 7.6) | 95 ( 7.0) | 367 ( 9.3) | 187 (11.4) |
| Hispanic | 3302 (14.8) | 769 (13.3) | 2017 (16.8) | 485 (17.4) | 1132 (17.9) | 247 (18.2) | 153 ( 3.9) | 37 ( 2.2) |
| Asian | 895 ( 4.0) | 402 ( 6.9) | 489 ( 4.1) | 236 ( 8.5) | 275 ( 4.4) | 124 ( 9.1) | 131 ( 3.3) | 42 ( 2.6 |
| Other | 1153 ( 5.2) | 302 ( 5.2) | 809 ( 6.7) | 199 ( 7.1) | 279 ( 4.4) | 89 ( 6.5) | 65 ( 1.6) | 14 ( ( |
| Not Reported | 148 ( 0.7) | 0 ( 0.0) | 82 ( 0.7) | 0 ( 0.0) | 64 ( 1.0) | 0 (0.0) | 2 ( 0.1) | 0 ( 0.0) |

*Notes:*
- Does not include 33 participants in the TIV/placebo group in Study AV003.
- Includes 171 recipients of FluMist at lower doses in Studies AV002 and AV002-2.
- Twelve participants from DMID #99-012 who received placebo at first visit and FluMist and second visit are included only in placebo columns.
- Sixty-four participants from Wyeth Study D145-P500 who received placebo at first visit and FluMist at a subsequent visit are included only in the placebo column.

## Table 49
## Demographic Characteristics of All High-Risk Participants at the Time of Initial Vaccination with FluMist or Placebo

| | Children (1–8 Years) | | Children & Adolescents (9–17 Years) | | Adults (18–64 Years) | | Adults (≥ 65 Years) | | Adults with COPD | |
|---|---|---|---|---|---|---|---|---|---|---|
| Characteristics | FluMist 765 | Placebo 13 | FluMist 540 | Placebo 24 | FluMist 65 | Placebo 42 | FluMist 131 | Placebo 101 | FluMist 1107 | Placebo 1108 |
| **Age (years)** | | | | | | | | | | |
| Median | 5.0 | 5.0 | 12.0 | 11.0 | 36.0 | 39.5 | 70.0 | 70.0 | 68.4 | 68.0 |
| Mean | 4.6 | 4.1 | 12.0 | 11.2 | 35.2 | 39.1 | 70.6 | 69.8 | 67.9 | 67.8 |
| Range | 1–8 | 1–7 | 9–17 | 9–17 | 18–58 | 20–58 | 65–87 | 65–75 | 50–90 | 50–91 |
| 25th percentile | 3 | 2 | 10 | 10 | 22 | 32 | 68 | 67 | 62 | 62 |
| 75th percentile | 6 | 6 | 14 | 13 | 46 | 46 | 73 | 72 | 74 | 74 |
| **Gender, %** | | | | | | | | | | |
| Male | 438 (57.3) | 6 (46.2) | 306 (56.7) | 12 (50.0) | 19 (29.2) | 26 (61.9) | 89 (67.9) | 67 (66.3) | 1085 (98.0) | 1090 (98.4) |
| Female | 326 (42.6) | 7 (53.8) | 234 (43.3) | 12 (50.0) | 46 (70.8) | 16 (38.1) | 42 (32.1) | 34 (33.7) | 22 ( 2.0) | 18 ( 1.6) |
| Not Reported | 1 ( 0.1) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | --- | --- |
| **Race/Ethnicity, %** | | | | | | | | | | |
| White | 532 (69.5) | 0 ( 0.0) | 410 (75.9) | 18 (75.0) | 35 (53.8) | 17 (40.5) | 121 (92.4) | 95 (94.1) | 922 (83.3) | 927 (83.7) |
| Black | 86 (11.2) | 10 (76.9) | 38 ( 7.0) | 2 ( 8.3) | 27 (41.5) | 20 (47.6) | 1 ( 0.8) | 3 ( 3.0) | --- | --- |
| Hispanic | 101 (13.2) | 2 (15.4) | 52 ( 9.6) | 1 ( 4.2) | 2 ( 3.1) | 2 ( 4.8) | 0 ( 0.0) | 0 ( 0.0) | --- | --- |
| Asian | 5 ( 0.7) | 0 ( 0.0) | 11 ( 2.0) | 2 ( 8.3) | 0 ( 0.0) | 2 ( 4.8) | 5 ( 3.8) | 3 ( 3.0) | --- | --- |
| Other | 31 ( 4.1) | 1 ( 7.7) | 16 ( 3.0) | 1 ( 4.2) | 1 ( 1.5) | 1 ( 2.4) | 4 ( 3.1) | 0 ( 0.0) | 185 (16.7) | 181 (16.3) |
| Not Reported | 10 ( 1.3) | 0 ( 0.0) | 13 ( 2.4) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | --- | --- |

*Note:* Thirteen participants from DMID #99-012 who received placebo at first visit and FluMist at second visit are included only in placebo column.

### 7.3.2. Overall Serious Adverse Events

SAEs reported by June 1, 2001, are summarized in Table 50.

**Table 50**
**SAEs in Completed Trials of FluMist by Age and Population**

| Population | FluMist | | Placebo | |
|---|---|---|---|---|
| | Number of SAEs | Number Enrolled | Number of SAEs | Number Enrolled |
| **1–8 Year Olds** | **60** | **12846** | **15** | **2829** |
| Healthy | 51 | 12069 | 14 | 2805 |
| Asthma | 7 | 754 | 0 | 0 |
| HIV-infected | 2 | 23 | 1 | 24 |
| **9–17 Year Olds** | **23** | **6861** | **1** | **1383** |
| Healthy | 21 | 6321 | 1 | 1359 |
| Asthma | 2 | 540 | 0 | 24 |
| **18–64 Year Olds** | **38** | **4012** | **25** | **1688** |
| Healthy | 38 | 3947 | 24 | 1646 |
| Asthma | 0 | 37 | 0 | 13 |
| HIV-infected | 0 | 28 | 1 | 29 |
| **≥65 Years of Age** | **2** | **131** | **2** | **101** |
| **Adults with COPD** | **290** | **1107** | **319** | **1108** |
| Total | 413 | 24957 | 362 | 7109 |

*Note:* Does not include SAEs from ongoing Study AV018.

Seven hundred seventy five SAEs have been reported from completed studies of FluMist; 609 (79%) of all SAEs were reported among adults with COPD (VA Study CSP #448) and 166 (21%) were reported from the remaining studies. Among the 775 SAEs in completed studies, 413 occurred in 24,957 FluMist recipients (1.6%) and 362 occurred in 7,109 placebo recipients (5.1%). An additional eight SAEs occurred in ongoing Study AV018.

Thirty-one of the 609 SAEs in the VA Study CSP #448 were considered vaccine related by the investigators prior to study unblinding (nine among 1,107 FluMist recipients and 22 among 1,108 placebo recipients).

In all other FluMist recipients, 60 SAEs occurred in children 1–8 years of age (51 in healthy children, seven in children with asthma and two in HIV-infected children); 23 occurred in children 9–17 years of age (21 in healthy children and two in children with a history of wheezing illness or asthma); 38 occurred in adults 18–64 years of age; and two occurred in adults ≥65 years of age.

Two SAEs in healthy children 14 months of age (in ongoing Study AV018 which are not included in Table 50) were determined to be related to vaccine (discussed in Section 7.3.2.2). Thus, of the 413 SAEs reported in FluMist recipients, 11 were judged related to vaccine (nine in adults with COPD and two in children 1–8 years of age).

### 7.3.2.1. Deaths

Sixty-five deaths occurred in clinical trials with FluMist. Two deaths occurred in healthy participants and 63 occurred in adults with COPD. One death due to drowning associated with alcohol intoxication occurred in a healthy adult 16 days after administration of FluMist in Study AV009; the event was not related to vaccine. One death occurred in a healthy child 18 months of age, 27 days after administration of the second dose which was administered six weeks after the first dose of FluMist in Wyeth Study D153-P500 conducted in South Africa. The child was taken to a clinic for investigation of the sudden onset of vomiting 24 days following the administration of the second dose of study vaccine. A diagnosis of bronchopneumonia was made and the child was treated with penicillin. Two days later, the child was taken to a hospital and the parents were advised to continue treatment. The same evening, the child began to have difficulty breathing and was taken the next day by ambulance to a hospital and administered IV antibiotics and oxygen but died shortly after admission (27 days after receipt of the second dose of study vaccine). The bronchopneumonia and death were assessed as unrelated to study vaccine.

The remaining 63 deaths occurred in adults with COPD in the VA Study CSP #448. The incidence of death in the VA Study CSP #448 was similar between FluMist and placebo mist recipients; 34 of the 63 deaths occurred in 1,107 FluMist recipients, while 29 occurred in 1,108 placebo recipients. Thirty-three of the 34 deaths in FluMist recipients were considered not related to study vaccine and one, a case of respiratory failure that occurred 218 days after vaccination, had no causality assessed and, therefore, was considered vaccine related. Prior to unblinding, three of the 29 deaths in the placebo group were considered vaccine related.

### 7.3.2.2. SAEs Possibly, Probably or Definitely Related to Study Treatment

There have been two vaccine related SAEs in two children 14 months of age who received FluMist and two vaccine-related SAEs in children 18 and 21 months of age who received placebo. A 14-month-old male participant received either FluMist or placebo at the time of the first study visit, and open-label FluMist at the time of his second visit. He presented six days after his second visit with acute onset of wheezing and cough. The child was diagnosed with

bronchiolitis and was treated with nebulized bronchodilators and an antibiotic and fully recovered. The SAE was assessed as medically important and possibly related to study vaccine. The participant had a history of bronchiolitis at five months of age.

A 14-month-old female participant received open-label FluMist for both the first and second doses of study product. The doses were administered 6 weeks apart. Twenty-one days after receipt of the second dose, she presented with fever, cough, and tachypnea, and was hospitalized with bronchiolitis and slight dehydration. She was treated with oral fluids and anti-pyretics. During the hospitalization, she was diagnosed with otitis *media* and treated with an antibiotic. She was discharged one day after admission; and her respiratory symptoms resolved within the next two days. The SAE was assessed as possibly related to study vaccine. Although there was no prior history of bronchiolitis, she was treated at 11 months of age with an antibiotic and salbutamol for a respiratory infection.

There have also been two vaccine-related SAEs in children 18 months and 21 months of age who after unblinding were noted to be placebo recipients. An 18-month-old female participant was admitted for croup four days after receiving her first dose of study product. She was treated with a steroid injection and nebulized epinephrine, and was discharged from the hospital to continue oral steroids for five days. The SAE was assessed as medically important and possibly related to study vaccine. The participant received placebo.

A 21-month-old female participant initially developed fever and difficulty breathing (stridor and/or wheezing) three days after receiving study product which recurred six days later. Acute laryngitis was diagnosed. The SAE was assessed as medically important and possibly related to study vaccine. The child was treated with nebulized epinephrine and steroids. The participant received placebo.

In adults, prior to unblinding to treatment group assignment, there were 31 vaccine related SAEs among 609 SAEs reported in 2,215 participants enrolled in the VA Study CSP #448. Among the 1,107 FluMist recipients in this trial, 215 experienced a total of 290 SAEs; nine were considered related to study product (eight reported as possibly related and one had an unknown relationship). Among the 1,108 placebo recipients, 217 experienced a total of 319 SAEs, 22 of which were considered as vaccine related (20 reported as possibly or probably related and two had an unknown relationship). Nearly all of the related events were respiratory in nature in this population of adults with COPD. There was one related event in the FluMist group that resulted in death; the event occurred 218 days after dosing and no causality was assessed by the investigator. In contrast, prior to unblinding there were three related events in the placebo

group in this population with COPD that resulted in three deaths; these events occurred on Day 3, 78, and 158.

### 7.3.3. Participants Withdrawn from Study Because of an Adverse Event

Three FluMist recipients 18–64 years of age withdrew or were withdrawn due to an adverse event following vaccination. All were unrelated to vaccination. The AEs were hypertension (Day 33 after vaccination, Study AV003), accidental drowning (Day 16 after vaccination, Study AV009), and cramping diarrhea (Day 2 after vaccination, Study AV009).

Two placebo recipients in Study AV006 Year One did not receive their second dose due to adverse events. One participant experienced wheezing one day post-vaccination that resolved four days later. Per discussion with the Principal Investigator, a decision was made to not give the second dose. However, this participant did return in the second year of the study (AV006 Year Two). Another participant did not receive the second dose as they were hospitalized 33 days post-vaccination for a shunt revision. Both of these participants were followed for the duration of Year One of the study for efficacy.

One child enrolled in Study AR001 who received FluMist was withdrawn from the study by the parents because of nasal congestion with onset the day following vaccination; the non-serious event was considered to be probably related to vaccination. The child completed the 42–day follow-up period following the first dose, but did not receive the second dose.

In Study DMID #99-012, the pediatric HIV study (designed as a crossover study), a parent commented on rapid breathing after a dose of FluMist and a dose of placebo mist in their child. This child did not receive the second dose of FluMist, but was not withdrawn from the study.

## 7.4. Safety in Healthy Adults (18–64 Years of Age)

### 7.4.1. Serious Adverse Events

SAEs are discussed in Section 7.3.2.

A total of 3,947 healthy FluMist recipients 18–64 years of age enrolled in Aviron studies (Table 48). Thirty-eight SAEs were reported in 4,012 FluMist recipients (<1%) and none were related to vaccination. Twenty-four SAEs were reported in 1,646 healthy adult placebo recipients (1.4%).

### 7.4.2. Demographics

The mean age was 37 years in the cohort of healthy adult FluMist and placebo recipients 18–64 years of age with reactogenicity event data (Table 51). There were slightly more female than male participants, and both treatment groups were predominantly white.

**Table 51**
**Demographic Characteristics of Healthy Adults 18–64 Years of Age with Reactogenicity Event Data**

| Characteristic | FluMist N=3666 | Placebo N=1646 |
|---|---|---|
| **Age (years)** | | |
| Median | 36.0 | 37.0 |
| Mean | 37.3 | 37.0 |
| 25th percentile | 29 | 29 |
| 75th percentile | 45 | 44 |
| Range | 18–64 | 18–64 |
| **Gender, n (%)** | | |
| Male | 1633 (44.5) | 754 (45.8) |
| Female | 2033 (55.5) | 892 (54.2) |
| **Race/Ethnicity, n (%)** | | |
| White | 3042 (83.0) | 1366 (83.0) |
| Black | 335 ( 9.1) | 187 (11.4) |
| Hispanic | 124 ( 3.4) | 37 ( 2.2) |
| Asian | 118 ( 3.2) | 42 ( 2.6) |
| Other | 47 ( 1.3) | 14 ( 0.9) |

### 7.4.3. Reactogenicity

The largest differences in reactogenicity rates between healthy FluMist and placebo recipients were seen for runny nose (43.7% versus 27.0%), and sore throat (26.2% versus 16.6%). The two treatment groups differed by <5% for all other reactogenicity events. Fever was uncommon in the seven days following vaccination and the rates of fever did not differ among FluMist (1.5%) and placebo (1.7%) recipients.

**Table 52**
**Reactogenicity Events (Days 0–7) in Healthy Adults 18–64 Years of Age by Treatment Group**

| Number of Participants Vaccinated | FluMist 3666 | Placebo 1646 |
|---|---|---|
| **Event** | **n/N (%)[a]** | **n/N (%)[a]** |
| Any event | 2527/3603 (70.1) | 984/1616 (60.9) |
| Cough | 488/3603 (13.5) | 173/1616 (10.7) |
| Runny nose | 1564/3576 (43.7) | 429/1589 (27.0) |
| Sore throat | 943/3603 (26.2) | 268/1616 (16.6) |
| Headache | 1326/3355 (39.5) | 559/1503 (37.2) |
| Chills | 285/3576 ( 8.0) | 95/1589 ( 6.0) |
| Muscle aches | 575/3603 (16.0) | 234/1616 (14.5) |
| Tired/Weak | 838/3328 (25.2) | 304/1476 (20.6) |
| Fever: | | |
| Temp >100°F | 54/3603 ( 1.5) | 27/1616 ( 1.7) |
| Temp >102°F | 3/3603 ( 0.1) | 2/1616 ( 0.1) |
| Temp >104°F | 0/3603 ( 0.0) | 0/1616 ( 0.0) |

[a] Percent calculated on number of participants with diary data available in studies in which the specific event was collected.

### 7.4.4. Reactogenicity by Gender

Overall, a higher proportion of females than males reported any reactogenicity events regardless of treatment group (FluMist: females, 75.1%; males 63.9%; placebo: females, 67.5%; males, 52.9%). The largest absolute differences between male and female FluMist recipients were seen for headache (12.7%), runny nose (7.1%), sore throat (6.4%) and tired/weak (6.1%). Similar differences were seen for these events between male and female placebo recipients.

**Table 53**
**Reactogenicity Events (Days 0–7) in Healthy Adults 18–64 Years of Age by Gender and Treatment Group**

| | Male | | Female | |
|---|---|---|---|---|
| Number of Participants Vaccinated | FluMist 1633 | Placebo 754 | FluMist 2033 | Placebo 892 |
| **Event** | **n/N (%)[a]** | **n/N (%)[a]** | **n/N (%)[a]** | **n/N (%)[a]** |
| Any event | 1016/1591 (63.9) | 388/733 (52.9) | 1511/2012 (75.1) | 596/883 (67.5) |
| Cough | 195/1591 (12.3) | 81/733 (11.1) | 293/2012 (14.6) | 92/883 (10.4) |
| Runny nose | 629/1582 (39.8) | 177/723 (24.5) | 935/1994 (46.9) | 252/866 (29.1) |
| Sore throat | 360/1591 (22.6) | 96/733 (13.1) | 583/2012 (29.0) | 172/883 (19.5) |
| Headache | 483/1488 (32.5) | 184/677 (27.2) | 843/1867 (45.2) | 375/826 (45.4) |
| Chills | 91/1582 ( 5.8) | 29/723 ( 4.0) | 194/1994 ( 9.7) | 66/866 ( 7.6) |
| Muscle aches | 218/1591 (13.7) | 101/733 (13.8) | 357/2012 (17.7) | 133/883 (15.1) |
| Tired/weak | 322/1479 (21.8) | 112/667 (16.8) | 516/1849 (27.9) | 192/809 (23.7) |
| Fever: | | | | |
| Temp >101°F | 18/1591 ( 1.1) | 10/733 ( 1.4) | 36/2012 ( 1.8) | 17/833 ( 1.9) |
| Temp >102°F | 2/1591 ( 0.1) | 0/733 ( 0.0) | 1/2012 ( 0.0) | 2/883 ( 0.2) |
| Temp >104°F | 0/1591 ( 0.0) | 0/733 ( 0.0) | 0/2012 ( 0.0) | 0/883 ( 0.0) |

[a] *Percent calculated on number of participants with diary data available in studies in which the specific event was collected.*

### 7.4.5. Reactogenicity by Race/Ethnicity

Rates of reactogenicity events in FluMist recipients varied slightly among the racial/ethnic groups, however no consistent relationships were apparent. FluMist recipients in each racial/ethnic group reported any reactogenicity event more frequently than placebo recipients.

## Table 54
## Reactogenicity Events (Days 0–7) in Healthy Adults 18–64 Years of Age by Race/Ethnicity Group

| | FluMist | | | | |
|---|---|---|---|---|---|
| | White | Black | Hispanic | Asian | Other |
| **Number of Participants** Vaccinated | 3042 | 335 | 124 | 118 | 47 |
| **Event** | **n/N (%)[a]** | **n/N (%)[a]** | **n/N (%)[a]** | **n/N (%)[a]** | **n/N (%)[a]** |
| Any event | 2128/3001 (70.9) | 200/320 (62.5) | 86/121 (71.1) | 77/115 (67.0) | 36/46 (78.3) |
| Cough | 390/3001 (13.0) | 49/320 (15.3) | 19/121 (15.7) | 22/115 (19.1) | 8/46 (17.4) |
| Runny nose | 1327/2980 (44.5) | 131/316 (41.5) | 51/120 (42.5) | 35/114 (30.7) | 20/46 (43.5) |
| Sore throat | 789/3001 (26.3) | 72/320 (22.5) | 35/121 (28.9) | 34/115 (29.6) | 13/46 (28.3) |
| Headache | 1134/2809 (40.4) | 92/286 (32.2) | 38/114 (33.3) | 43/101 (42.6) | 19/45 (42.2) |
| Chills | 214/2980 ( 7.2) | 39/316 (12.3) | 13/120 (10.8) | 12/114 (10.5) | 7/46 (15.2) |
| Muscle aches | 461/3001 (15.4) | 57/320 (17.8) | 28/121 (23.1) | 20/115 (17.4) | 9/46 (19.6) |
| Tired/Weak | 694/2788 (24.9) | 60/282 (21.3) | 36/113 (31.9) | 28/100 (28.0) | 20/45 (44.4) |
| Fever: | | | | | |
| Temp >100°F | 35/3001 ( 1.2) | 12/320 ( 3.8) | 4/121 ( 3.3) | 2/115 ( 1.7) | 1/46 ( 2.2) |
| Temp >102°F | 1/3001 ( 0.0) | 2/320 ( 0.6) | 0/121 ( 0.0) | 0/115 ( 0.0) | 0/46 ( 0.0) |
| Temp >104°F | 0/3001 ( 0.0) | 0/320 ( 0.0) | 0/121 ( 0.0) | 0/115 ( 0.0) | 0/46 ( 0.0) |
| | **Placebo** | | | | |
| | White | Black | Hispanic | Asian | Other |
| **Number of Participants** Vaccinated | 1366 | 187 | 37 | 42 | 14 |
| **Event** | **n/N (%)[a]** | **n/N (%)[a]** | **n/N (%)[a]** | **n/N (%)[a]** | **n/N (%)[a]** |
| Any event | 831/1346 (61.7) | 103/180 (57.2) | 18/36 (50.0) | 23/42 (54.8) | 9/12 (75.0) |
| Cough | 139/1346 (10.3) | 26/180 (14.4) | 3/36 (8.3) | 3/42 ( 7.1) | 2/12 (16.7) |
| Runny nose | 360/1329 (27.1) | 50/172 (29.1) | 7/35 (20.0) | 9/41 (22.0) | 3/12 (25.0) |
| Sore throat | 229/1346 (17.0) | 23/180 (12.8) | 5/36 (13.9) | 7/42 (16.7) | 4/12 (33.3) |
| Headache | 486/1255 (38.7) | 49/167 (29.3) | 8/32 (25.0) | 12/37 (32.4) | 4/12 (33.3) |
| Chills | 81/1329 ( 6.1) | 12/172 ( 7.0) | 2/35 ( 5.7) | 0/41 ( 0.0) | 0/12 ( 0.0) |
| Muscle aches | 190/1346 (14.1) | 27/180 (15.0) | 8/36 (22.2) | 4/42 (9.5) | 5/12 (41.7) |
| Tired/Weak | 261/1238 (21.1) | 30/159 (18.9) | 6/31 (19.4) | 7/36 (19.4) | 0/12 ( 0.0) |
| Fever: | | | | | |
| Temp >100°F | 20/1346 ( 1.5) | 7/180 ( 3.9) | 0/36 ( 0.0) | 0/42 ( 0.0) | 0/12 ( 0.0) |
| Temp >102°F | 2/1346 ( 0.1) | 0/180 ( 0.0) | 0/36 ( 0.0) | 0/42 ( 0.0) | 0/12 ( 0.0) |
| Temp >104°F | 0/1346 ( 0.0) | 0/180 ( 0.0) | 0/36 ( 0.0) | 0/42 ( 0.0) | 0/12 ( 0.0) |

[a] Percent calculated on number of participants with diary data available in studies in which the specific event was collected.

### 7.4.6. Number of Days and by Day Analysis of Reactogenicity

Among healthy adults, 3,041 of the 3,666 were enrolled in the placebo controlled trial, Study AV009. Analyses were performed to define the number of days of specific reactogenicity events in the seven days following vaccination in healthy adults 18–64 years of age in Study AV009. Figure 3 presents these data for the number of days with runny nose and Figure 4 presents the "by day" data for runny nose. Similarly, Figure 5 and Figure 6 present these data for sore throat in healthy adults.

Most vaccinees had no days of runny nose (56%), but more placebo recipients had no days of runny nose (73%) (Figure 3). The "by day" analysis showed that after vaccination, vaccinees had significantly more runny nose than placebo recipients on days one to five (Figure 4). Similarly, most vaccinees had no days of sore throat (73%), but placebo recipients had even fewer (84%) (Figure 5). The "by day" analysis showed that vaccinees had significantly more sore throat than placebo recipients on days one to three after vaccination (Figure 6).

**Figure 3**
**Number of Days with Runny Nose in Adults in Study AV009 with Onset Day 0–7**

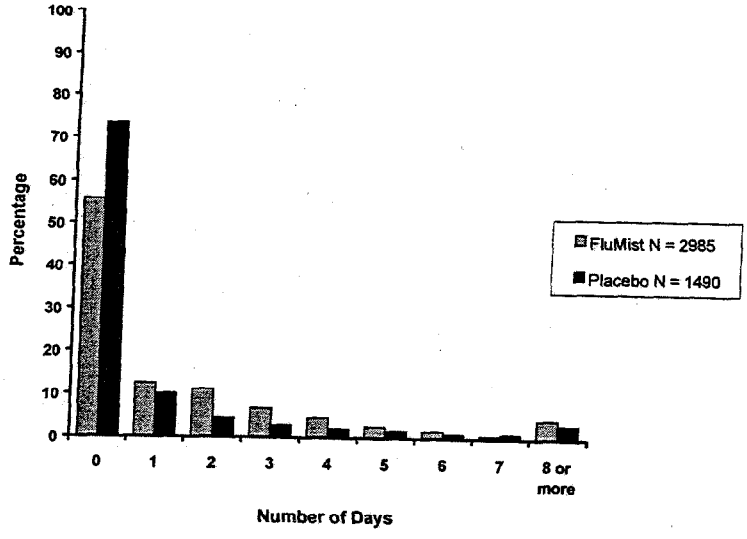


**Figure 4**
**Proportion of Adults with Runny Nose in Study AV009 by Day Analysis**

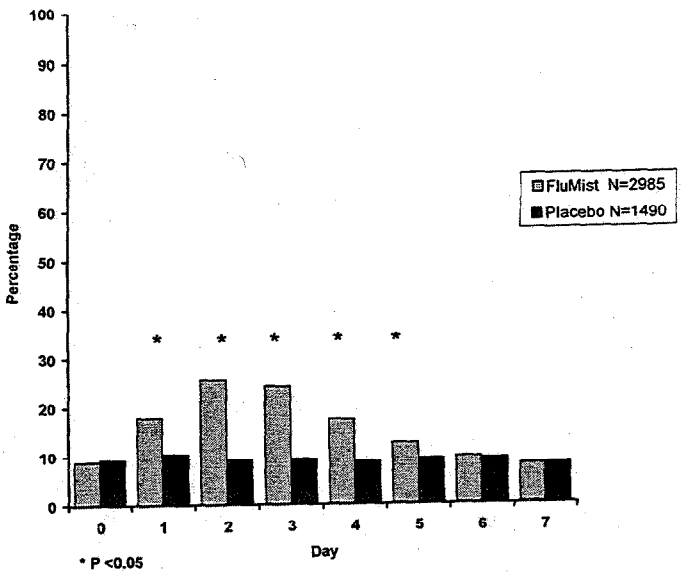



**Figure 5**
**Number of Days with Sore Throat in Adults in Study AV009 with Onset Day 0–7**

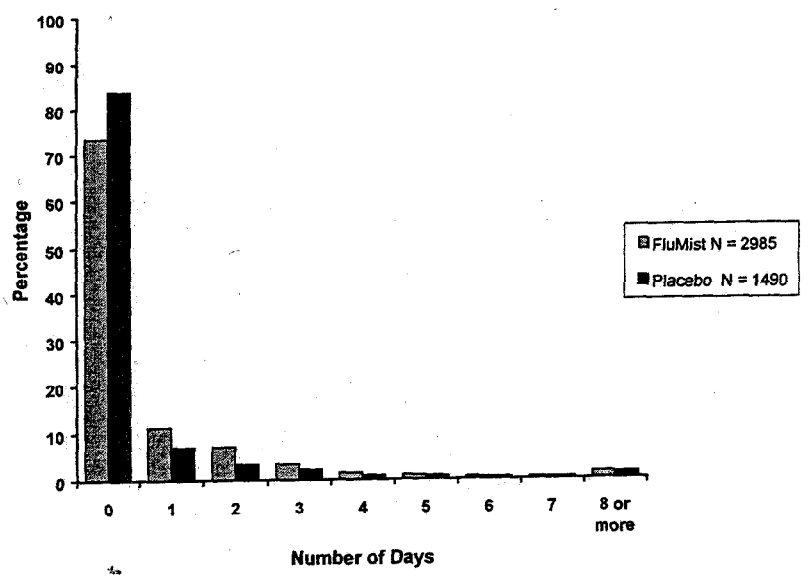
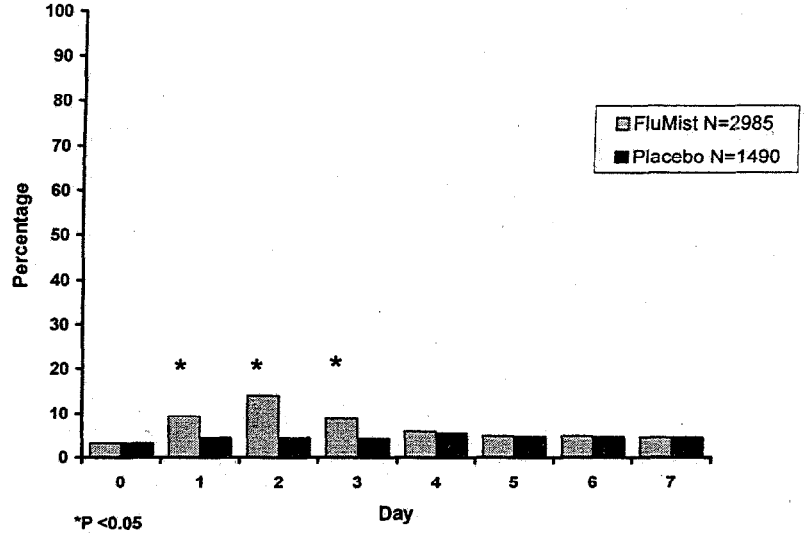


**Figure 6**
**Proportion of Adults with Sore Throat in Study AV009**
**by Day Analysis with Onset Day 0–7**




### 7.4.7. Other Analyses During the Reactogenicity Period

#### 7.4.7.1. Illness Event Complexes During the Reactogenicity Period

In addition to the protocol specific analyses, additional analyses were performed for defined illness event complexes (Table 55). There was a 7.4% increase in FluMist recipients over placebo in the illness event complex defined as three or more reactogenicity events on the same day. There was a 0.3% increase over placebo in the CDC-Influenza-Like Illness defined complex. In both vaccinees and placebo recipients no one met the illness event complex defined as fever, cough, and runny nose. These data are consistent with the low rate of fever in the seven days following vaccination in Study AV009 (1.34% in both vaccinees and placebo recipients).

**Table 55**
**Proportion of Healthy Adults 18–64 Years of Age in Study AV009 with Illness Event Complexes in the 7 Day Post-Vaccination Period**

| Number Returning Diary Cards | FluMist N=2985 | Placebo N=1490 | |
|---|---|---|---|
| **Participants with:** | **%** | **%** | **p-value[a]** |
| 3 or more events[b] | 19.5 | 12.1 | <0.01 |
| CDC-ILI[c] | 1.1 | 0.8 | 0.43 |
| Fever[d], cough, and runny nose/ nasal congestion | 0 | 0 | 1.00 |

[a] Fisher's Exact test.
[b] Events occurred on same day.
[c] Defined as temperature ≥100°F plus cough or sore throat on either the same or consecutive days.
[d] Temperature ≥100°F.

### 7.4.7.2. Medication Use During the Reactogenicity Period

Participants recorded all medication use on the seven day diary following vaccination. These data are presented in Table 56. The differences between treatment groups were not significantly different for antibiotic use, analgesic/antipyretic use, or for use of antihistamines/antitussives/ decongestants.

**Table 56**
**Proportion of Healthy Adults with Medication Use in Study AV009 in the 7-Day Post-Vaccination Period**

| Number Vaccinated | FluMist N=3041 | Placebo N=1520 | |
|---|---|---|---|
| **Medication** | **%** | **%** | **P-value[a]** |
| Antibiotics-(oral) | 1.6 | 1.1 | 0.29 |
| Analgesics/antipyretics | 26.1 | 23.9 | 0.10 |
| Antihistamines/anti-tussives/decongestants | 9.0 | 8.0 | 0.29 |

[a] Fisher's Exact test.

### 7.4.7.3. Otitis Media in the Reactogenicity Period

The occurrence of otitis media in the seven days following vaccination was rare. One adult FluMist recipient out of 3,041 vaccinees (0.03%) reported otitis media compared to one out of 1,520 placebo recipients (0.06%).

### 7.4.7.4. Other Adverse Events

Overall, FluMist recipients were more likely to report adverse events than placebo recipients (30.4% versus 22.0%) (Table 57). Respiratory symptoms, including nasal congestion, rhinitis, and sinusitis, occurred more frequently in FluMist (17.7%) than placebo (7.8%) recipients. No differences were found in the type or frequency of adverse events for any other body systems.

**Table 57**
**Adverse Events (Days 0–7) in Healthy Adults 18–64 Years of Age by Treatment Group**

| | FluMist N=3666 | Placebo N=1646 |
|---|---|---|
| **Any Adverse Event, n (%)** | **1114 (30.4)** | **362 (22.0)** |
| **Body System** | | |
| Preferred Term | **n (%)** | **n (%)** |
| **Body As A Whole** | 258 ( 7.0) | 100 ( 6.1) |
| Headache | 60 ( 1.6) | 21 ( 1.3) |
| Pain abdominal | 28 ( 0.8) | 18 ( 1.1) |
| Pain back | 19 ( 0.5) | 19 ( 1.2) |
| **Digestive** | 197 ( 5.4) | 96 ( 5.8) |
| Diarrhea | 73 ( 2.0) | 37 ( 2.2) |
| Nausea | 61 ( 1.7) | 31 ( 1.9) |
| Dyspepsia | 43 ( 1.2) | 24 ( 1.5) |
| **Respiratory** | 650 (17.7) | 129 ( 7.8) |
| Congestion nasal | 317 ( 8.6) | 33 ( 2.0) |
| Rhinitis | 236 ( 6.4) | 58 ( 3.5) |
| Sinusitis | 138 ( 3.8) | 31 ( 1.9) |
| **Urogenital** | 44 ( 1.2) | 20 ( 1.2) |
| Dysmenorrhea | 37 ( 1.0) | 17 ( 1.0) |

*Note:* Includes only adverse events occurring in ≥1% of participants.

### 7.4.8. Summary

Three thousand nine hundred forty-seven healthy adults 18–64 years of age have received at least one dose of FluMist. FluMist was safe and well-tolerated in these healthy adults 18–64 years of age. No SAEs related to FluMist have been reported in healthy adults 18–64 years of age. The administration of FluMist was associated with a 17% increase (44% versus 27%) in the frequency of runny nose compared to placebo and a 9% increase in sore throat (26% versus 17%). All other differences were <5%.

## 7.5. Safety in Healthy Children (1–8 Years of Age)

### 7.5.1. Serious Adverse Events – Initial Vaccination Year

SAEs are discussed in Section 7.3.2.

In completed trials with FluMist, 51 SAEs have been reported in 12,069 healthy FluMist recipients 1–8 years of age (0.4%) and 14 SAEs have been reported in 2,805 placebo recipients (0.5%). None of these SAEs were vaccine-related. In the ongoing Study AV018, two vaccine-related SAEs after FluMist administration have been reported in healthy children. These are discussed in Section 7.3.2.2.

### 7.5.2. Demographics

For studies of FluMist where reactogenicity was collected, the demographic profile of healthy children 1–8 years of age who received FluMist is presented in Table 58.

**Table 58**
**Demographic Characteristics of Healthy Children (1–8 Years of Age) with Reactogenicity Event Data at Time of First Vaccination**

| Characteristic | FluMist N=2355 | Placebo N=720 |
|---|---|---|
| **Age (years)** | | |
| Median | 3.0 | 3.0 |
| Mean | 3.2 | 3.0 |
| Range | 1–8 | 1–8 |
| 25th *percentile* | 2 | 2 |
| 75th percentile | 4 | 4 |
| **Gender, n (%)** | | |
| Female | 1183 (50.2) | 365 (50.7) |
| Male | 1172 (49.8) | 355 (49.3) |
| **Race/Ethnicity, n (%)** | | |
| Asian | 20 ( 0.8) | 4 ( 0.6) |
| Black | 199 ( 8.5) | 76 (10.6) |
| Hispanic | 277 (11.8) | 79 (11.0) |
| Other | 73 ( 3.1) | 16 ( 2.2) |
| White | 1786 (75.8) | 545 (75.7) |

### 7.5.3. Reactogenicity During Initial Vaccination Year

FluMist was well-tolerated in healthy children 1–8 years of age. A slightly larger proportion of FluMist recipients than placebo recipients reported any reactogenicity event following Dose One (71.6% versus 65.3%) (Table 59). In general, participants in both treatment groups reported reactogenicity less frequently following Dose Two; the proportion of participants reporting any reactogenicity event decreased more in the FluMist group (71.6% down to 59.4%) than in the placebo group (65.3% down to 59.4%).

The largest absolute difference observed between FluMist and placebo recipients reporting any individual event following Dose One was for runny nose/nasal congestion (9.6%) (Table 59). Between FluMist and placebo recipients following Dose One or Dose Two, all other differences in specific reactogenicity events including fever (temperature >100°F, oral equivalent), were <5%.

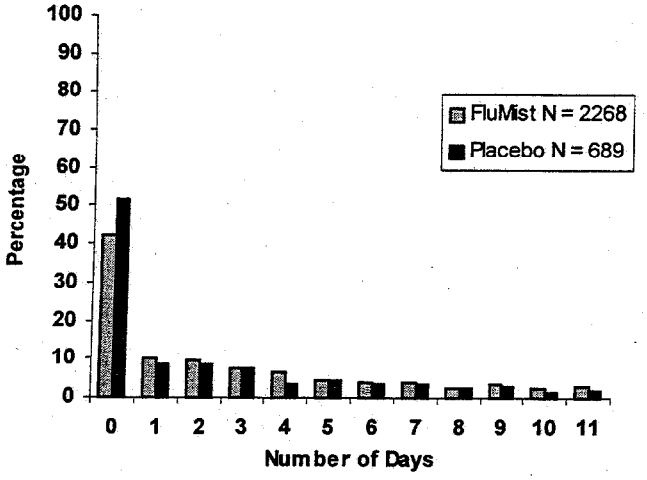
**Table 59**
**Reactogenicity Events (Days 0–10) in Healthy Children 1–8 Years of Age Following Initial Vaccination by Dose and Treatment Group**

| | Post-Dose One | | Post-Dose Two | |
|---|---|---|---|---|
| **Number of participants vaccinated** | **FluMist** 2355 | **Placebo** 720 | **FluMist** 1985 | **Placebo** 570 |
| **Event** | **n/N (%)** | **n/N (%)** | **n/N (%)** | **n/N (%)** |
| Any event | 1668/2330 (71.6) | 469/718 (65.3) | 1171/1971 (59.4) | 336/566 (59.4) |
| Cough | 626/2330 (26.9) | 206/718 (28.7) | 540/1971 (27.4) | 164/566 (29.0) |
| Runny nose/ Nasal congestion | 1290/2240 (57.6) | 331/689 (48.0) | 834/1943 (42.9) | 239/566 (42.2) |
| Sore throat | 234/2330 (10.0) | 62/718 ( 8.6) | 131/1971 ( 6.6) | 42/566 ( 7.4) |
| Irritability | 606/2302 (26.3) | 185/718 (25.8) | 338/1943 (17.4) | 108/566 (19.1) |
| Headache | 215/2268 ( 9.5) | 49/689 ( 7.1) | 121/1971 ( 6.1) | 36/566 ( 6.4) |
| Chills | 95/2268 ( 4.2) | 28/689 ( 4.1) | 70/1971 ( 3.6) | 13/566 ( 2.3) |
| Vomiting | 152/2240 ( 6.8) | 30/689 ( 4.4) | 117/1943 ( 6.0) | 25/566 ( 4.4) |
| Muscle aches | 113/2268 ( 5.0) | 24/689 ( 3.5) | 55/1971 ( 2.8) | 16/566 ( 2.8) |
| Decreased activity | 360/2240 (16.1) | 90/689 (13.1) | 242/1943 (12.5) | 67/566 (11.8) |
| Fever: | | | | |
| Temp 1: >100°F, oral equivalent | 383/2330 (16.4) | 88/718 (12.3) | 222/1971 (11.3) | 57/566 (10.1) |
| Temp 2: >102°F, oral equivalent | 67/2330 ( 2.9) | 25/718 ( 3.5) | 46/1971 ( 2.3) | 20/566 ( 3.5) |
| Temp 3: >104°F, oral equivalent | 1/2330 ( 0.0) | 1/718 ( 0.1) | 5/1971 ( 0.3) | 3/566 ( 0.5) |

*Note:* Percent calculated on number of participants with diary data available in studies in which the specific event was collected.

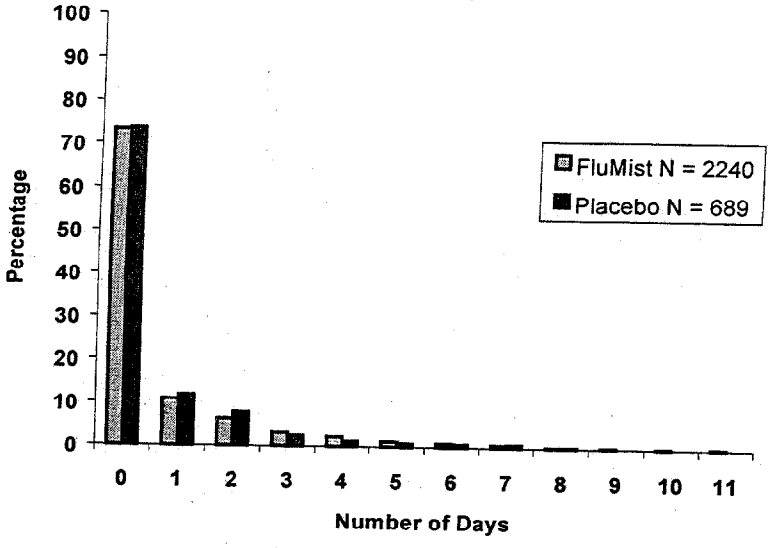
Analyses were performed to define the number of days with each event and the incidence of specific reactogenicity events on each of the 10 days following initial vaccination in healthy children 1–8 years of age. Figures 7–10 present the number of days for runny nose/nasal congestion, irritability, decreased activity, and fever and Figures 11–14 present the "by day" analyses. More placebo recipients than vaccinees had no days of runny nose/nasal congestion, irritability, decreased activity or fever >100°F (Figures 7–10). Fever, irritability, and decreased activity peaked on Day 2 after vaccination (Figures 11–14). Runny nose/nasal congestion peaked on Days 3 and 8 in about 30% of FluMist recipients (Figure 11), the other three events occurred in 10% or less of vaccinees on a given day (Figures 12–14).

**Figure 7**
**Number of Days of Runny Nose/Nasal Congestion during the 10-Day Reactogenicity Period Post-Dose One in Children 1–8 Years of Age**



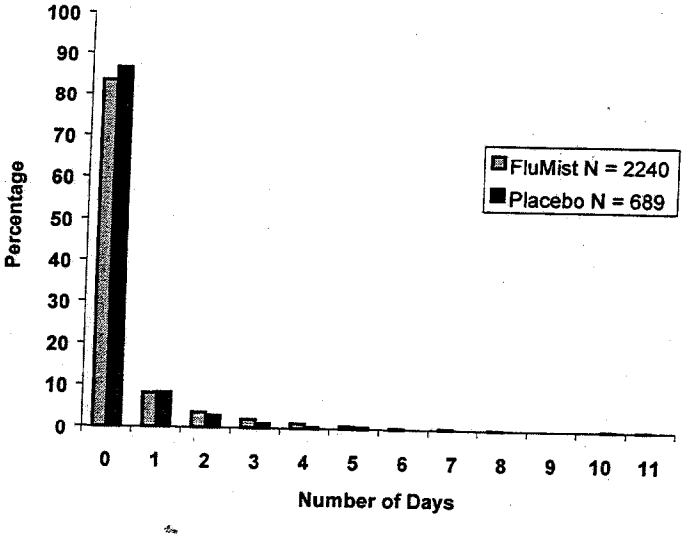

Note: Data for studies with 10-day symptom card collection are presented.

**Figure 8**
**Number of Days of Irritability during the 10-Day Reactogenicity Period Post-Dose One in Children 1–8 Years of Age**



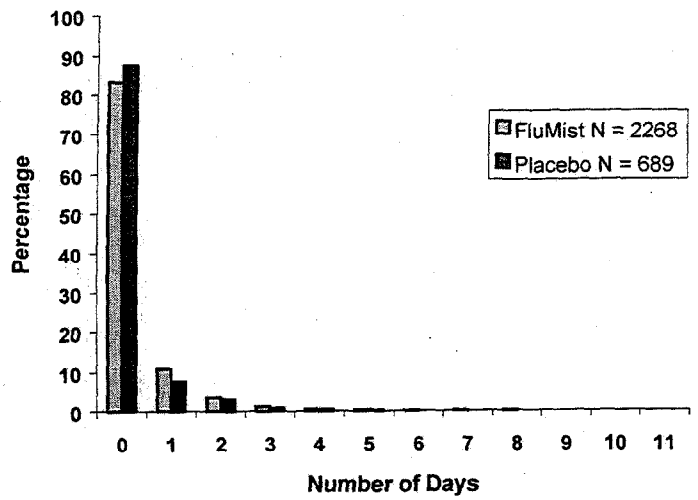

Note: Data for studies with 10-day symptom card collection are presented.

**Figure 9**
**Number of Days of Decreased Activity during the 10-Day Reactogenicity Period Post-Dose One in Children 1–8 Years of Age**



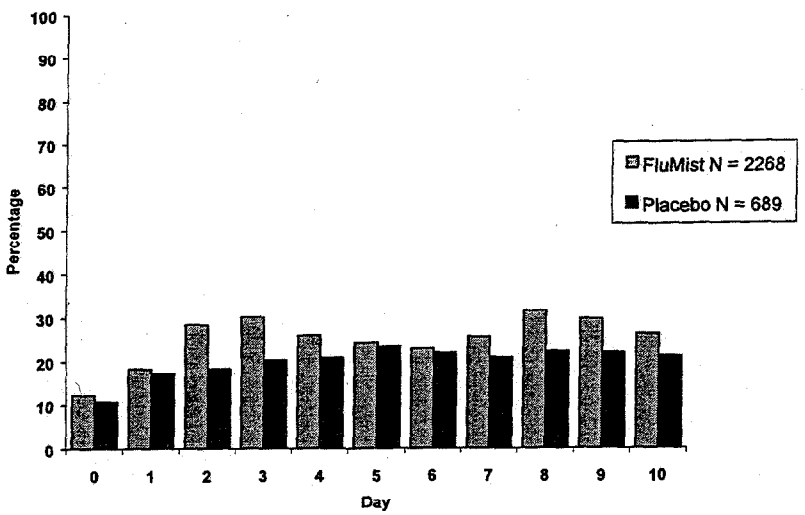

Note: Data for studies with 10-day symptom card collection are presented.

**Figure 10**
**Number of Days of Fever >100°F during the 10-Day Reactogenicity Period Post-Dose One in Children 1–8 Years of Age**



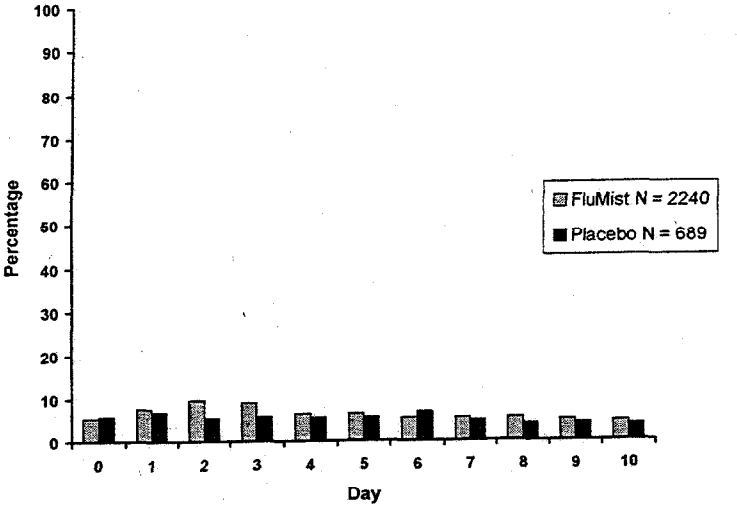

Note: Data for studies with 10-day symptom card collection are presented.

**Figure 11**
**Proportion of Healthy Children 1–8 Years of Age with Runny Nose/Nasal Congestion Following Dose One by Day with Onset Day 0–10**



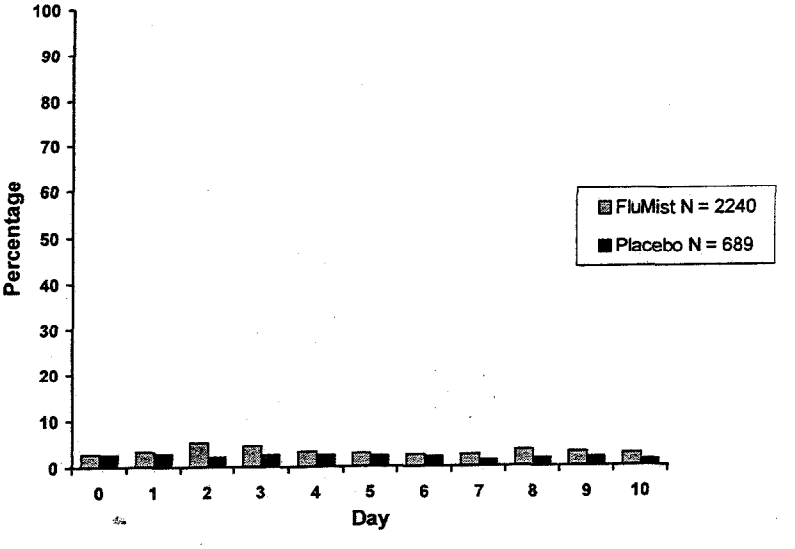

Note: Data for studies with 10-day symptom card collection are presented.

**Figure 12**
**Proportion of Healthy Children 1–8 Years of Age with Irritability Following Dose One by Day with Onset Day 0–10**



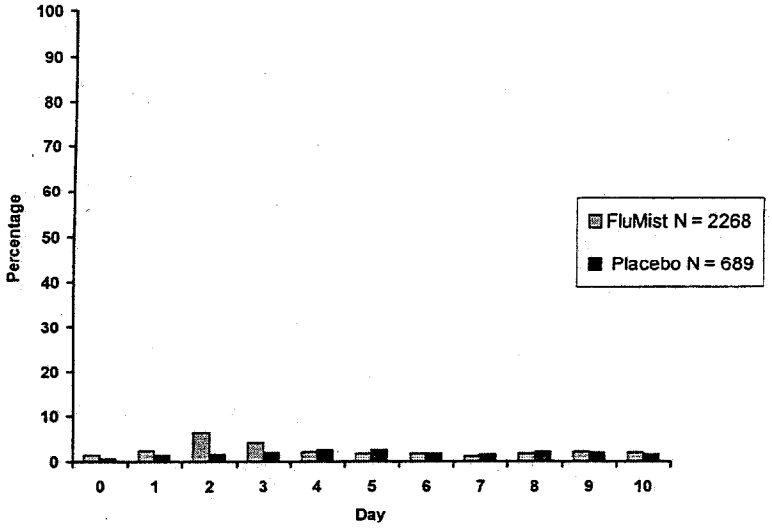

Note: Data for studies with 10-day symptom card collection are presented.

**Figure 13**
**Proportion of Healthy Children 1–8 Years of Age with Decreased Activity Following Dose One by Day with Onset Day 0–10**




Note: Data for studies with 10-day symptom card collection are presented.

**Figure 14**
**Proportion of Healthy Children 1–8 Years of Age with Fever Following Dose One by Day with Onset Day 0–10**




Note: Data for studies with 10-day symptom card collection are presented.

### 7.5.4. Other Analyses During the Reactogenicity Period

#### 7.5.4.1. Illness Event Complexes During the Reactogenicity Period

In addition to the protocol specific analyses, additional analyses were performed for defined illness event complexes (Table 60). Following Dose One, there was a 5.9% increase over placebo in the illness event complex defined as three or more reactogenicity events on the same day. There was a 1.2% increase over placebo in the CDC-Influenza-Like Illness defined complex. Similarly, there was a 1.5% increase over placebo in the illness event complex defined as temperature ≥100°F oral, with cough, and runny nose/nasal congestion. Following Dose Two, all three illness event complexes were higher in the placebo groups.

**Table 60**
**Proportion of Healthy Children 1–8 Years of Age with Illness Event Complexes during the Reactogenicity Period in Placebo Controlled Studies**

| | Dose One | | Dose Two | |
|---|---|---|---|---|
| | FluMist | Placebo | FluMist | Placebo |
| Number Returning Diary Cards | 1682 | 718 | 1379 | 566 |
| **Participants with:** | % | % | % | % |
| 3 or more events[a] | 22.2* | 16.3 | 16.5 | 17.1 |
| CDC-ILI[b] | 6.9 | 5.7 | 5.9 | 6.9 |
| Fever[c], cough, and runny nose/nasal congestion | 3.2 | 1.7 | 2.5 | 3.4 |

*Note:* The reactogenicity period for Studies AV006 and AV007 was Day 0–10 and for AV002 and AV002-2 was Day 0–7.

[a] Events occurred on same day.

[b] Defined as temperature ≥100°F on a single day plus cough or sore throat on either the same or consecutive days.

[c] Temperature ≥100°F.

* $p<0.05$.

### 7.5.4.2. Medication Use During the Reactogenicity Period

Parents/guardians recorded all medication use on the 7 or 10 day diary following vaccination. These data are presented in Table 61.

Antipyretic/analgesic use was approximately 5.3% higher in the vaccinees and is consistent with the higher incidence of low grade fever following Dose One of FluMist (Table 59). This difference was not observed after Dose Two. The rates of antibiotic use and antihistamines/antitussives/ decongestants use were similar between treatment groups across both doses.

**Table 61**
**Proportion of Healthy Children 1–8 Years of Age with Medication Use during the Reactogenicity Period in Placebo Controlled Trials**

| | Dose One | | Dose Two | |
|---|---|---|---|---|
| | FluMist N=1704 | Placebo N=754 | FluMist N=1233 | Placebo N=513 |
| Medication | % | % | % | % |
| Antibiotic (oral) | 5.2 | 4.1 | 5.9 | 5.1 |
| Antihistamines/Antitussives/ Decongestants | 17.2 | 16.3 | 15.9 | 17.9 |
| Antipyretics/Analgesics | 21.8[a] | 16.5 | 12.5 | 13.5 |
| Beta Agonist/Glucocorticoids (nasal/oral) | 0.5 | 0.5 | 1.1 | 0.8 |

*Note:* The reactogenicity period for Studies AV006 and AV007 was Day 0–10 and for AV002 and AV002-2 was Day 0–7.

[a] $p<0.05$.

### 7.5.4.3. Otitis Media During the Reactogenicity Period

Table 62 presents the occurrence of otitis media within the 7 to 10 day post-vaccination period in several placebo-controlled trials in children 1–8 years of age. The occurrence of otitis media between the two treatment groups was not different.

**Table 62**
**Proportion of Healthy Children 1–8 Years of Age with Otitis Media during the Reactogenicity Period in Placebo-Controlled Trials**

| Group | FluMist % | Placebo % | P value[a] |
|---|---|---|---|
| AV006 Year One | | | |
| Dose One | 1.59 | 1.37 | 0.66 |
| Dose Two | 3.16 | 1.91 | 0.27 |
| AV006 Year Two | 1.53 | 1.36 | 1.00 |
| AV007 | | | |
| Dose One | 1.25 | 2.00 | 0.63 |
| Dose Two | 1.32 | 0.00 | 0.59 |
| AV002 | 2.27 | 0.00 | 1.00 |
| AV002-2 | 0.00 | 11.1 | 0.32 |

*Note:* The reactogenicity period for Studies AV006 and AV007 was Day 0–10 and for AV002 and AV002-2 was Day 0–7.

[a] Fisher's exact test vaccine versus placebo for any given dose of vaccine.

### 7.5.5. Other Adverse Events – Initial Vaccination Year

Table 63 summarizes adverse events other than reactogenicity events occurring in ≥1% of healthy children 1–8 years of age in either treatment group.

For individual adverse events, no rate differences greater than 2% were noted between FluMist and placebo recipients. Overall, adverse events occurred in 20.3% and 16.4% of FluMist and placebo recipients, respectively, following Dose One and in 14.6% and 14.7% of FluMist and placebo recipients, respectively, following Dose Two.

**Table 63**
**Adverse Events (Days 0–10) Following Initial Vaccination in Healthy Children 1–8 Years of Age**

| | Post-Dose One | | Post-Dose Two | |
|---|---|---|---|---|
| | **FluMist** | **Placebo** | **FluMist** | **Placebo** |
| | N=2355 | N=720 | N=1985 | N=570 |
| **Any Adverse Event, n (%)** | **479 (20.3)** | **118 (16.4)** | **289 (14.6)** | **84 (14.7)** |
| **Body System** | | | | |
| *Preferred Term* | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| **Body As A Whole** | 173 ( 7.3) | 49 ( 6.8) | 81 ( 4.1) | 31 ( 5.4) |
| Pain | 40 ( (1.7) | 18 ( 2.5) | 10 ( 0.5) | 7 ( 1.2) |
| Pain Abdominal | 39 ( 1.7) | 5 ( 0.7) | 19 ( 1.0) | 2 ( 0.4) |
| Infection | 32 ( 1.4) | 10 ( 1.4) | 22 ( 1.1) | 7 ( 1.2) |
| Injury Accidental | 26 ( 1.1) | 5 ( 0.7) | 14 ( 0.7) | 7 ( 1.2) |
| **Digestive** | 122 ( 5.2) | 33 ( 4.6) | 76 ( 3.8) | 23 ( 4.0) |
| Diarrhea | 74 ( 3.1) | 23 ( 3.2) | 55 ( 2.8) | 15 ( 2.6) |
| Anorexia | 24 ( 1.0) | 5 ( 0.7) | 16 ( 0.8) | 4 ( 0.7) |
| **Skin** | 48 ( 2.0) | 17 ( 2.4) | 45 ( 2.3) | 7 ( 1.2) |
| Rash | 29 ( 1.2) | 12 ( 1.7) | 30 ( 1.5) | 3 ( 0.5) |
| **Special Senses** | 83 ( 3.5) | 15 ( 2.1) | 67 ( 3.4) | 15 ( 2.6) |
| Otitis Media | 34 ( 1.4) | 9 ( 1.3) | 38 ( 1.9) | 9 ( 1.6) |
| Pain ear | 24 ( 1.0) | 3 ( 0.4) | 10 ( 0.5) | 3 ( 0.5) |

*Note:* Includes only adverse events occurring in ≥1% of participants.

### 7.5.6. Reactogenicity by Age

Age was associated with reactogenicity risk among FluMist recipients for certain reactogenicity events. Following Dose One, runny nose/nasal congestion, fever, and irritability decreased with increasing age. In contrast, sore throat and headache increased with age (Table 64). These age-related patterns may reflect the increasing ability of older children to verbalize symptoms. Similar reactogenicity patterns by age for fever, irritability, sore throat, and headache were also observed in placebo recipients. These patterns were seen following Dose Two although the overall rates of reactogenicity were decreased.

## Table 64
## Reactogenicity Events on Days 0–10 Following Dose One in Healthy Children 1–8 Years of Age, by Age and Treatment Group

| Event | Age in Months | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 12–23 months | | 24–35 months | | 36–47 months | | 48–59 months | | 60–107 months | |
| | FluMist N=484 n/N (%)[a] | Placebo N=162 n/N (%)[a] | FluMist N=565 n/N (%)[a] | Placebo N=176 n/N (%)[a] | FluMist N=365 n/N (%)[a] | Placebo N=108 n/N (%)[a] | FluMist N=361 n/N (%)[a] | Placebo N=130 n/N (%)[a] | FluMist N=580 n/N (%)[a] | Placebo N=144 n/N (%)[a] |
| Any event | 390/479 (81.4) | 121/161 (75.2) | 422/560 (75.4) | 113/176 (64.2) | 263/361 (72.9) | 61/107 (57.0) | 227/356 (63.8) | 82/130 (63.1) | 366/574 (63.8) | 92/144 (63.9) |
| Cough | 132/479 (27.6) | 47/161 (29.2) | 147/560 (26.3) | 45/176 (25.6) | 101/361 (28.0) | 31/107 (29.0) | 94/356 (26.4) | 35/130 (26.9) | 152/574 (26.5) | 48/144 (33.3) |
| Runny nose/ Nasal congestion | 325/473 (68.7) | 83/159 (52.2) | 340/542 (62.7) | 81/167 (48.5) | 205/345 (59.4) | 47/101 (46.5) | 174/341 (51.0) | 57/124 (46.0) | 246/539 (45.6) | 63/138 (45.7) |
| Sore throat | 25/479 ( 5.2) | 11/161 ( 6.8) | 44/560 ( 7.9) | 9/176 ( 5.1) | 37/361 (10.2) | 2/107 ( 1.9) | 37/356 (10.4) | 13/130 (10.0) | 91/574 (15.9) | 27/144 (18.8) |
| Irritability | 205/477 (43.0) | 71/161 (44.1) | 185/557 (33.2) | 47/176 (26.7) | 84/360 (23.3) | 20/107 (18.7) | 54/352 (15.3) | 24/130 (18.5) | 78/556 (14.0) | 23/144 (16.0) |
| Headache | 23/475 ( 4.8) | 5/159 ( 3.1) | 31/545 ( 5.7) | 2/167 ( 1.2) | 29/346 ( 8.4) | 3/101 ( 3.0) | 30/345 ( 8.7) | 18/124 (14.5) | 102/557 (18.3) | 21/138 (15.2) |
| Chills | 16/475 ( 3.4) | 9/159 ( 5.7) | 26/545 ( 4.8) | 5/167 ( 3.0) | 9/346 ( 2.6) | 4/101 ( 4.0) | 15/345 ( 4.3) | 4/124 ( 3.2) | 29/557 ( 5.2) | 6/138 ( 4.3) |
| Vomiting | 42/473 ( 8.9) | 10/159 ( 6.3) | 39/542 ( 7.2) | 9/167 ( 5.4) | 25/345 ( 7.2) | 3/101 ( 3.0) | 16/341 ( 4.7) | 5/124 ( 4.0) | 30/539 ( 5.6) | 3/138 ( 2.2) |
| Muscle aches | 15/475 ( 3.2) | 7/159 ( 4.4) | 23/545 ( 4.2) | 3/167 ( 1.8) | 19/346 ( 5.5) | 3/101 ( 3.0) | 23/345 ( 6.7) | 5/124 ( 4.0) | 33/557 ( 5.9) | 6/138 ( 4.3) |
| Decreased activity | 80/473 (16.9) | 29/159 (18.2) | 102/542 (18.8) | 20/167 (12.0) | 49/345 (14.2) | 10/101 ( 9.9) | 61/341 (17.9) | 14/124 (11.3) | 68/539 (12.6) | 17/138 (12.3) |
| Fever: | | | | | | | | | | |
| Temp 1: Oral >100°F | 96/479 (20.0) | 30/161 (18.6) | 121/560 (21.6) | 24/176 (13.6) | 58/361 (16.1) | 7/107 ( 6.5) | 49/356 (13.8) | 13/130 (10.0) | 59/574 (10.3) | 14/144 ( 9.7) |
| Temp 2: Oral >102°F | 17/479 ( 3.5) | 16/161 ( 9.9) | 21/560 ( 3.8) | 4/176 ( 2.3) | 7/361 ( 1.9) | 2/107 ( 1.9) | 13/356 ( 3.7) | 1/130 ( 0.8) | 9/574 ( 1.6) | 2/144 ( 1.4) |
| Temp 3: Oral >104°F | 1/479 ( 0.2) | 0/161 ( 0.0) | 0/560 ( 0.0) | 1/176 ( 0.6) | 0/361 ( 0.0) | 0/107 ( 0.0) | 0/356 ( 0.0) | 0/130 ( 0.0) | 0/574 ( 0.0) | 0/144 ( 0.0) |

[a] Percent calculated on number of participants with diary data available in studies in which the specific event was collected.

### 7.5.7. Reactogenicity by Gender

There were no clinically important differences observed in the rate with which reactogenicity events occurred among males and females following Dose One of vaccine or placebo (Table 65). Similar results were observed following Dose Two (data not shown).

**Table 65**
**Reactogenicity Events (Days 0–10) Following Dose One in Healthy Children 1–8 Years of Age by Gender**

| | Post-Dose One | | | |
|---|---|---|---|---|
| | Male | | Female | |
| Event | FluMist N=1172 n/N (%)[a] | Placebo N=355 n/N (%)[a] | FluMist N=1183 n/N (%)[a] | Placebo N=365 n/N (%)[a] |
| Any event | 834/1161 (71.8) | 233/354 (65.8) | 834/1169 (71.3) | 236/364 (64.8) |
| Cough | 318/1161 (27.4) | 112/354 (31.6) | 308/1169 (26.3) | 94/364 (25.8) |
| Runny nose/Nasal congestion | 647/1113 (58.1) | 163/339 (48.1) | 643/1127 (57.1) | 168/350 (48.0) |
| Sore throat | 122/1161 (10.5) | 28/354 ( 7.9) | 112/1169 ( 9.6) | 34/364 ( 9.3) |
| Irritability | 302/1149 (26.3) | 94/354 (26.6) | 304/1153 (26.4) | 91/364 (25.0) |
| Headache | 103/1125 ( 9.2) | 14/339 ( 4.1) | 112/1143 ( 9.8) | 35/350 (10.0) |
| Chills | 50/1125 ( 4.4) | 17/339 ( 5.0) | 45/1143 ( 3.9) | 11/350 ( 3.1) |
| Vomiting | 83/1113 ( 7.5) | 18/339 ( 5.3) | 69/1127 ( 6.1) | 12/350 ( 3.4) |
| Muscle aches | 54/1125 ( 4.8) | 11/339 ( 3.2) | 59/1143 ( 5.2) | 13/350 ( 3.7) |
| Decreased activity | 177/1113 (15.9) | 46/339 (13.6) | 183/1127 (16.2) | 44/350 (12.6) |
| Fever: | | | | |
| Temp 1: Oral >100°F | 198/1161 (17.1) | 47/354 (13.3) | 185/1169 (15.8) | 41/364 (11.3) |
| Temp 2: Oral >102°F | 34/1161 ( 2.9) | 14/354 ( 4.0) | 33/1169 ( 2.8) | 11/364 ( 3.0) |
| Temp 3: Oral >104°F | 1/1161 ( 0.1) | 1/354 ( 0.3) | 0/1169 ( 0.0) | 0/364 ( 0.0) |

[a] Percent calculated on number of participants with diary data available in studies in which the specific event was collected.

### 7.5.8. Reactogenicity by Race/Ethnicity

The reactogenicity of FluMist appears to be consistent across race/ethnicity groups, although limited data for some groups make it difficult to reach definitive conclusions (Table 66).

## Table 66
## Reactogenicity Events (Days 0–10) Following Dose One in Healthy Children 1–8 Years of Age by Race/Ethnicity

| | FluMist | | | | |
|---|---|---|---|---|---|
| | White N=1786 | Black N=199 | Hispanic N=277 | Asian N=20 | Other N=73 |
| Event | n/N (%) | n/N (%) | n/N (%) | n/N (%) | n/N (%) |
| Any event | 1277/1768 (72.2) | 132/197 (67.0) | 190/273 (69.6) | 18/20 (90.0) | 51/72 (70.8) |
| Cough | 474/1768 (26.8) | 55/197 (27.9) | 70/273 (25.6) | 7/20 (35.0) | 20/72 (27.8) |
| Runny nose/ Nasal congestion | 979/1715 (57.1) | 104/185 (56.2) | 147/248 (59.3) | 17/20 (85.0) | 43/72 (59.7) |
| Sore throat | 185/1768 (10.5) | 20/197 (10.2) | 23/273 ( 8.4) | 1/20 ( 5.0) | 5/72 ( 6.9) |
| Irritability | 475/1745 (27.2) | 35/195 (17.9) | 75/270 (27.8) | 6/20 (30.0) | 15/72 (20.8) |
| Headache | 157/1738 ( 9.0) | 18/187 ( 9.6) | 32/251 (12.7) | 2/20 (10.0) | 6/72 ( 8.3) |
| Chills | 69/1738 ( 4.0) | 7/187 ( 3.7) | 17/251 ( 6.8) | 0/20 ( 0.0) | 2/72 ( 2.8) |
| Vomiting | 106/1715 ( 6.2) | 20/185 (10.8) | 23/248 ( 9.3) | 0/20 ( 0.0) | 3/72 ( 4.2) |
| Muscle aches | 90/1738 ( 5.2) | 6/187 ( 3.2) | 14/251 ( 5.6) | 1/20 ( 5.0) | 2/72 ( 2.8) |
| Decreased activity | 283/1715 (16.5) | 31/185 (16.8) | 31/248 (12.5) | 2/20 (10.0) | 13/72 (18.1) |
| Fever: | | | | | |
| Temp. 1: Oral >100°F | 290/1768 (16.4) | 34/197 (17.3) | 41/273 (15.0) | 2/20 (10.0) | 16/72 (22.2) |
| Temp. 2: Oral >102°F | 45/1768 ( 2.5) | 6/197 ( 3.0) | 10/273 ( 3.7) | 0/20 ( 0.0) | 6/72 ( 8.3) |
| Temp. 3: Oral >104°F | 0/1768 ( 0.0) | 1/197 ( 0.5) | 0/273 ( 0.0) | 0/20 ( 0.0) | 0/72 ( 0.0) |
| | Placebo | | | | |
| | White N=545 | Black N=76 | Hispanic N=79 | Asian N=4 | Other N=16 |
| Event | n/N (%) | n/N (%) | n/N (%) | n/N (%) | n/N (%) |
| Any event | 362/543 (66.7) | 45/76 (59.2) | 50/79 (63.3) | 2/4 (50.0) | 10/16 (62.5) |
| Cough | 154/543 (28.4) | 21/76 (27.6) | 23/79 (29.1) | 2/4 (50.0) | 6/16 (37.5) |
| Runny nose/ Nasal congestion | 251/527 (47.6) | 31/73 (42.5) | 38/69 (55.1) | 2/4 (50.0) | 9/16 (56.3) |
| Sore throat | 45/543 ( 8.3) | 5/76 ( 6.6) | 11/79 (13.9) | 0/4 ( 0.0) | 1/16 ( 6.3) |
| Irritability | 148/543 ( 27.3) | 15/76 (19.7) | 20/79 (25.3) | 1/4 (25.0) | 1/16 ( 6.3) |
| Headache | 35/527 ( 6.6) | 8/73 (11.0) | 5/69 ( 7.2) | 0/4 ( 0.0) | 1/16 ( 6.3) |
| Chills | 19/527 ( 3.6) | 4/73 ( 5.5) | 3/69 ( 4.3) | 1/4 (25.0) | 1/16 ( 6.3) |
| Vomiting | 23/527 ( 4.4) | 2/73 ( 2.7) | 4/69 ( 5.8) | 0/4 ( 0.0) | 1/16 ( 6.3) |
| Muscle aches | 16/527 ( 3.0) | 4/73 ( 5.5) | 4/69 ( 5.8) | 0/4 ( 0.0) | 0/16 ( 0.0) |
| Decreased activity | 70/527 (13.3) | 10/73 (13.7) | 9/69 (13.0) | 0/4 ( 0.0) | 1/16 ( 6.3) |
| Fever: | | | | | |
| Temp. 1: Oral >100°F | 69/543 (12.7) | 10/76 (13.2) | 8/79 (10.1) | 1/4 (25.0) | 0/16 ( 0.0) |
| Temp. 2: Oral >102°F | 20/543 ( 3.7) | 0/76 ( 0.0) | 4/79 ( 5.1) | 1/4 (25.0) | 0/16 ( 0.0) |
| Temp. 3: Oral >104°F | 1/543 ( 0.2) | 0/76 ( 0.0) | 0/79 ( 0.0) | 0/4 ( 0.0) | 0/16 ( 0.0) |

### 7.5.9. Safety of Annual Administration of FluMist in Children (1–8 Years of Age)

Children were enrolled over multiple seasons in two studies. In Study AV006, children received FluMist or placebo for two consecutive years and were eligible for re-enrollment for a third year in Study AV015 and for a fourth year in Study AV017. In Study AV012, children were eligible for enrollment over three study seasons. Based on these two study populations, 2,729 children received FluMist in a second season, 1,219 for a third season, and 539 for a fourth season. Seven SAEs occurred following a second annual vaccination and one SAE occurred after the third and fourth annual vaccinations, respectively. None were vaccine related.

#### 7.5.9.1. Demographics of Participants Receiving Fourth Annual Re-vaccination

The demographics of children enrolled for four consecutive years of annual vaccination (those children who participated in both years of Study AV006 and were enrolled in Study AV015 and Study AV017) are presented in Table 67. A total of 549 children 1–8 years of age at the time of initial dosing in Year One received one or more doses of FluMist in each of four consecutive years. More than 90% of the participants were White (Table 67). Except for race/ethnicity, these participants are demographically similar to the overall healthy FluMist recipients 1–8 years of age (Table 48). The mean age of three years reflects the age at the time of dosing in the first year of the trial in Study AV006. At enrollment in Study AV017, these participants were three years older and ranged in age from 4–9 years with a mean of approximately 6 years.

**Table 67**
**Demographic Characteristics of Healthy Children 1–8 Years of Age Receiving at Least One Dose of FluMist in Four Consecutive Years**

| Characteristic | N=549 |
|---|---|
| **Age (years)**[a] | |
| Median | 3.0 |
| Mean | 3.0 |
| Range | 1–5 |
| 25th percentile | 2 |
| 75th percentile | 4 |
| **Gender, n (%)** | |
| Female | 292 (53.2) |
| Male | 257 (46.8) |
| **Race/Ethnicity, n (%)** | |
| White | 499 (90.9) |
| Asian | 3 ( 0.5) |
| Black | 30 ( 5.5) |
| Hispanic | 6 ( 1.1) |
| Other | 11 ( 2.0) |

[a] Age at time of initial vaccination in Study AV006.

### 7.5.9.2. Serious Adverse Events – Fourth Annual Re-vaccination

SAEs are discussed in Section 7.3.2. One SAE in a FluMist recipient, was reported in Study AV017 in the fourth year of vaccination. The SAE was not vaccine related.

### 7.5.9.3. Reactogenicity Over Four Years

Among the 549 children who received one or more doses of FluMist in four consecutive years, the proportion reporting any reactogenicity event or any specific reactogenicity event was similar in the second, third, and fourth years (Table 68).

**Table 68**
**Reactogenicity Events (Days 0–10) in Healthy Children 1–8 Years of Age Receiving at Least One Dose of FluMist in Four Consecutive Years**

| | 1st Year (AV006) | | 2nd Year (AV006) | 3rd Year (AV015) | 4th Year (AV017) |
|---|---|---|---|---|---|
| | Dose One[a] | Dose Two | One Dose | One Dose | One Dose |
| **Number of Participants** | | | | | |
| Vaccinated | 549 | 479 | 549 | 549 | 549 |
| With Diary Data Available | 547 | 477 | 547 | 548 | 545 |
| **Event** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Any event | 401 (73) | 335 (70) | 308 (56) | 301 (55) | 275 (50) |
| Cough | 141 (26) | 169 (35) | 137 (25) | 148 (27) | 148 (27) |
| Runny nose/Nasal congestion | 315 (58) | 248 (52) | 227 (41) | 200 (36) | 204 (37) |
| Sore throat | 44 ( 8) | 29 ( 6) | 49 ( 9) | 42 ( 8) | 62 (11) |
| Irritability | 127 (23) | 74 (16) | 76 (14) | 48 ( 9) | 52 (10) |
| Headache | 41 ( 7) | 26 ( 5) | 48 ( 9) | 54 (10) | 62 (11) |
| Chills | 11 ( 2) | 14 ( 3) | 18 ( 3) | 12 ( 2) | 11 ( 2) |
| Vomiting | 29 ( 5) | 40 ( 8) | 21 ( 4) | 29 ( 5) | 18 ( 3) |
| Muscle aches | 23 ( 4) | 15 ( 3) | 14 ( 3) | 13 ( 2) | 24 ( 4) |
| Decreased activity | 78 (14) | 52 (11) | 57 (10) | 50 ( 9) | 52 (10) |
| Fever: | | | | | |
| Temp 1: oral >100°F | 79 (14) | 53 (11) | 58 (11) | 50 ( 9) | 39 ( 7) |
| Temp 2: oral >101°F | 28 ( 5) | 20 ( 4) | 31 ( 6) | 17 ( 3) | 19 ( 3) |
| Temp 3: oral >102°F | 11 ( 2) | 9 ( 2) | 15 ( 3) | 8 ( 1) | 11 ( 2) |
| Temp 4: oral >103°F | 4 ( 1) | 3 ( 1) | 7 ( 1) | 4 ( 1) | 5 ( 1) |
| Temp 5: oral >104°F | 1 (<1) | 0 ( 0) | 2 (<1) | 0 ( 0) | 1 (<1) |

[a] Two-Dose and One-Dose Regimen are combined.

### 7.5.9.4. Other Adverse Events Over Four Years

Of the children who were vaccinated with FluMist for four consecutive years, 11.8% experienced adverse events in the fourth year (Table 69). No single adverse event was reported by more than 0.9% of participants in the fourth year of vaccination. In general, adverse events were less frequent in the second, third, and fourth years compared to the first year.

**Table 69**
**Adverse Events (Days 0–10) in Healthy Children 1–8 Years of Age Receiving at Least One Dose of FluMist in Four Consecutive Years**

| | 1st Year (AV006) | | 2nd Year (AV006) | 3rd Year (AV015) | 4th Year (AV017) |
|---|---|---|---|---|---|
| | Dose One[a] | Dose Two | One Dose | One Dose | One Dose |
| | N=549 | N=479 | N=549 | N=549 | N=549 |
| **Any Adverse Event, n (%)** | **102 (18.6)** | **64 (13.4)** | **80 (14.6)** | **79 (14.4)** | **65 (11.8)** |
| **Body System** | | | | | |
| Preferred Term | n (%) | n (%) | n (%) | n (%) | n (%) |
| **Body as a whole** | **54 ( 9.8)** | **19 ( 4.0)** | **32 ( 5.8)** | **31 ( 5.6)** | **19 ( 3.5)** |
| Allergic reaction | 8 ( 1.5) | 0 ( 0.0) | 6 ( 1.1) | 2 ( 0.4) | 2 ( 0.4) |
| Infection | 10 ( 1.8) | 6 ( 1.3) | 1 ( 0.2) | 0 ( 0.0) | 0 ( 0.0) |
| Infection viral | 3 ( 0.5) | 1 ( 0.2) | 1 ( 0.2) | 6 ( 1.1) | 0 ( 0.0) |
| Injury accidental | 11 ( 2.0) | 3 ( 0.6) | 11 ( 2.0) | 6 ( 1.1) | 3 ( 0.5) |
| Pain | 15 ( 2.7) | 2 ( 0.4) | 6 ( 1.1) | 1 ( 0.2) | 5 ( 0.9) |
| Pain abdominal | 6 ( 1.1) | 4 ( 0.8) | 2 ( 0.4) | 14 ( 2.6) | 5 ( 0.9) |
| **Digestive** | **30 ( 5.5)** | **16 ( 3.3)** | **14 ( 2.6)** | **17 ( 3.1)** | **11 ( 2.0)** |
| Anorexia | 8 ( 1.5) | 5 ( 1.0) | 0 ( 0.0) | 2 ( 0.4) | 0 ( 0.0) |
| Diarrhea | 22 ( 4.0) | 10 ( 2.1) | 8 ( 1.5) | 9 ( 1.6) | 5 ( 0.9) |
| **Respiratory** | **9 ( 1.6)** | **14 ( 2.9)** | **19 ( 3.5)** | **16 ( 2.9)** | **18 ( 3.3)** |
| Epistaxis | 3 ( 0.5) | 5 ( 1.0) | 5 ( 0.9) | 3 ( 0.5) | 3 ( 0.5) |
| Sneezing | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 7 ( 1.3) | 5 ( 0.9) |
| **Skin** | **3 ( 0.5)** | **5 ( 1.0)** | **8 ( 1.5)** | **8 ( 1.5)** | **4 ( 0.7)** |
| Rash | 1 ( 0.2) | 3 ( 0.6) | 6 ( 1.1) | 4 ( 0.7) | 3 ( 0.5) |
| **Special senses** | **10 ( 1.8)** | **22 ( 4.6)** | **14 ( 2.6)** | **20 ( 3.6)** | **9 ( 1.6)** |
| Conjunctivitis | 2 ( 0.4) | 5 ( 1.0) | 1 ( 0.2) | 6 ( 1.1) | 4 ( 0.7) |
| Otitis media | 4 ( 0.7) | 13 ( 2.7) | 8 ( 1.5) | 9 ( 1.6) | 3 ( 0.5) |
| Pain ear | 4 ( 0.7) | 2 ( 0.4) | 4 ( 0.7) | 6 ( 1.1) | 2 ( 0.4) |

*Note:* *Excludes reactogenicity events beginning within ten days after vaccination. Includes only adverse events occurring in ≥1% of participants in any treatment group.*

[a] Two-Dose and One-Dose Regimen are combined.

### 7.5.10. Summary

Among healthy children 1–8 years of age, FluMist was well-tolerated with a 4.1% increase (16.4% versus 12.3%) in the rate of low grade fever (temperature >100°F) and a 9.6% increase (57.6% versus 48.0%) in the rate of runny nose/nasal congestion compared to placebo after Dose One (Table 59). Following Dose One, antipyretics/analgesics were used more often in vaccinees. In general, reactogenicity events were reported less frequently following the second dose than after the first dose. This would be expected to occur if immunity induced by Dose

One reduced vaccine virus replication following Dose Two. Other adverse events were reported infrequently. The incidence of otitis media was not significantly increased in vaccinees in the post-vaccination reactogenicity period. Two SAEs related to FluMist in children younger than nine years of age have been reported; two children 14 months of age developed wheezing or bronchiolitis after dosing with FluMist.

Annual administration of FluMist was safe and well-tolerated in healthy children 1–8 years of age. The proportions of FluMist recipients reporting reactogenicity events decreased with repetitive dosing. SAEs were rare following re-vaccination.

### 7.6. Safety in Healthy Children and Adolescents (9–17 Years of Age)

#### 7.6.1. Serious Adverse Events

SAEs are presented in Section 7.3.2.

A total of 6,321 healthy children and adolescents 9–17 years of age have received at least one dose of FluMist. Twenty-one SAEs were reported in 6,321 FluMist recipients (0.33%) and none were considered related to vaccine.

#### 7.6.2. Demographics

The mean age of FluMist recipients with reactogenicity events in this population was 11 years, approximately one-half were female, and 73.6% were white.

#### 7.6.3. Reactogenicity and Other Adverse Events

Nearly all children and adolescents 9–17 years of age were enrolled in either Study AV012 or AV019 which did not collect reactogenicity events or other non-serious adverse events. Reactogenicity events and other non-serious adverse events with onset from Day 0–7 after vaccination in this age group were collected from 72 FluMist and 11 placebo recipients. These data are not presented here due to the limited sample size. The event rates were similar to those observed in children 1–8 and adults 18–64 years of age.

#### 7.6.4. Summary

FluMist was safe and well-tolerated among healthy children and adolescents 9–17 years of age.

## 7.7. Safety in Healthy Children and Adolescents 1–17 Years of Age in Study AV019: Interim Data

### 7.7.1. Study Design

Study AV019 is a prospective, randomized, double-blind, placebo controlled trial to assess safety. Healthy children 1 to 17 years of age who were members of the Kaiser Permanente Medical Care Program of Northern California (KP) were eligible to enroll. The trial was initiated in October 2000. All SAEs recorded as of June 1, 2001 and all medically attended events (MAEs) recorded in the KP medical utilization database as of December 31, 2000 are presented in this interim summary; this includes 88% of expected follow-up after Dose One and approximately 43% of expected follow-up after Dose Two. Participants were randomized 2:1 to receive FluMist or placebo. Children younger than 9 years of age at entry were to receive two doses of FluMist or placebo one month apart and children 9 years of age and older were to receive one dose.

The primary objective was to estimate the rates of all MAEs, including SAEs and pre-specified grouped diagnoses, within 42 days following the administration of FluMist compared to the rates following administration of placebo. The pre-specified grouped diagnoses were groups of related MAEs that could potentially be caused by influenza infection and included:

- acute respiratory tract events;
- systemic bacterial infections;
- acute gastrointestinal tract events; and
- rare events potentially related to influenza.

The specific diagnostic terms that comprised each of the pre-specified grouped diagnoses are listed in Appendix 1.

### 7.7.2. Statistical Methods

A binomial analysis of each MAE was the primary test. Event rates (per 1,000 person months) by treatment group, relative risks (FluMist rates divided by placebo rates), and exact, two-sided 90% mid-probability binomial confidence intervals, adjusted for follow-up time, were constructed. The binomial analysis is a "participant-incidence" approach: multiple health care provider encounters for the same MAE experienced by a given participant were counted only once.

A statistically significantly increased risk in the FluMist group was defined by a lower bound of the confidence interval greater than one. A statistically significantly decreased risk in the FluMist group was defined by an upper bound of the confidence interval less than one.

A secondary analysis using Poisson regression which includes multiple encounters per participant was also performed. These results are not presented because nearly all participants reporting events had only one encounter per diagnosis. Furthermore, the conclusions based upon the Poisson analysis did not differ from those based upon the binomial analysis.

Statistical analysis was performed for each reported MAE diagnosis by each of three utilization settings: the hospital; the outpatient clinic; and the emergency department (ED). For the individual MAEs that comprised the four pre-specified grouped diagnoses (Appendix 1), analyses were performed for all utilization settings combined. The pre-specified grouped diagnoses were analyzed for all utilization settings combined and for each individual utilization setting.

Percents of participants with MAEs are provided in the text for descriptive purposes. Percents were computed without adjusting for censoring of follow-up time.

More than 1,500 statistical comparisons were performed in this analysis without adjustment for multiple comparisons. Therefore, it is highly likely that statistically significant treatment differences were observed due to chance alone.

### 7.7.3. Enrollment

A total of 9,689 evaluable participants were included in this summary (Table 70). Of this total, 5,637 (58%) were 1–8 years of age, and 4,052 (42%) were 9–17 years of age at entry. Six thousand four hundred seventy-three (67%) participants received FluMist, and 3,216 (33%) received placebo.

**Table 70**
**Enrollment by Age and Treatment Group for the 9,689 Evaluable Participants**

| Age in Years | Treatment Group | | Total N (%) |
|---|---|---|---|
| | FluMist N (%) | Placebo N (%) | |
| 1–8 | 3769 (39) | 1868 (19) | 5637 (58) |
| 9–17 | 2704 (28) | 1348 (14) | 4052 (42) |
| Total | 6473 (67) | 3216 (33) | 9689 (100) |

### 7.7.4. Demographics

The study population was equally distributed by gender (49% male), and was racially/ethnically diverse; approximately 55% of participants were White, 20% Hispanic, 10% Asian or Pacific Islander, 6% Black, 4.5% Multiracial, 0.1% American Indian, and 4% Other.

The mean age at entry for both FluMist and placebo recipients was 8.1 years, and the median age was 7.8 and 7.7 years for FluMist and placebo recipients, respectively.

### 7.7.5. Overview Of Safety

A low rate of SAEs among FluMist recipients was observed in this study [13 SAEs among the 6,473 vaccinees (0.2%)] and is consistent with the low rate of SAEs in prior Aviron studies. No SAEs in this large study were considered related to vaccine.

In the analysis of MAEs, overall medical utilization for FluMist and placebo recipients was similar in each of the three utilization settings (Table 71).

**Table 71**
**Number and Percent of Participants Who Experienced an MAE, by Utilization Setting and Treatment Group**

| Utilization Setting | FluMist N=6473 | Placebo N=3216 |
|---|---|---|
| | n (%) | n (%) |
| Hospital | 23 ( 0.4) | 14 ( 0.4) |
| ED | 141 ( 2.2) | 75 ( 2.3) |
| Clinic | 1812 (28.0) | 905 (28.1) |

None of the four pre-specified grouped diagnoses occurred more frequently in FluMist recipients compared with placebo recipients following Dose One, Dose Two, or after all doses combined, in all utilization settings combined (Table 72). When the pre-specified grouped diagnoses were analyzed for the individual utilization settings, acute respiratory tract events were significantly increased in the ED following Dose One for participants 1–17 years of age and for participants 9–17 years of age, and acute gastrointestinal tract events were significantly increased in the ED for participants 9–17 years of age. In contrast, acute gastrointestinal tract events were significantly decreased in the clinic and all utilization settings combined following Dose One for participants 12–17 months, 1–8 years, and 1–17 years of age.

Increases in the rates for individual MAEs for which an association with FluMist was observed were balanced by a similar number of MAEs that were decreased in FluMist recipients. Events associated with an increased relative risk for FluMist recipients included conjunctivitis, URI, asthma, otitis media with effusion (OME), acute respiratory tract events, abdominal pain, acute gastrointestinal tract events, musculoskeletal pain, cellulitis, benign lesion, enuresis, speech delay, UTI, seborrhea, and otitis externa (Table 73).

Events associated with a decreased relative risk for FluMist recipients included cough, tonsillitis, wheezing, wheezing/shortness of breath (SOB), abdominal pain, acute gastroenteritis, constipation, acute gastrointestinal tract events, febrile illness, viral syndrome, gingivitis, trauma, vision disorder, and well care/reassurance/follow-up (Table 74).

Some of these outcomes were likely due to chance alone given the large number of comparisons.

#### 7.7.5.1. Serious Adverse Events (SAEs)

SAEs are discussed in Section 7.3.2. SAEs occurred at a rate of 0.2% and were proportionately distributed between FluMist (N=13) and placebo (N=7) recipients. None of the 13 SAEs reported in FluMist recipients were judged related to study vaccine.

#### 7.7.5.2. Medically Attended Events (MAEs)

In the analysis of MAEs, none of the four pre-specified grouped diagnoses: acute respiratory tract events, systemic bacterial infections, acute gastrointestinal tract events, or rare events, potentially related to influenza, occurred more frequently in FluMist recipients compared with placebo recipients in any of the age groups (12 to 17 months, 18 to 35 months, 1 to 8 years, 9 to 17 years, or 1 to 17 years) and after any of the doses (following Dose One, following Dose Two, or following all doses combined) in the analyses of all utilization settings combined (Table 72). When the pre-specified grouped diagnoses were analyzed for the individual utilization settings, acute respiratory tract events were significantly increased in the ED following Dose One for participants 1–17 years of age and for participants 9–17 years of age, and acute gastrointestinal tract events were significantly increased in the ED for participants 9–17 years of age. In contrast, acute gastrointestinal tract events were significantly decreased in the clinic and all utilization settings combined following Dose One for participants 12–17 months, 1–8 years, and 1–17 years of age.

**Table 72**
**Rates and Relative Risks for the Pre-Specified Grouped Diagnoses, All Ages, All Doses and All Utilization Settings Combined**

| Pre-Specified Group Diagnosis | Number of Participants | | Rate per 1000-Person Months[a] FluMist/Placebo | Binomial Relative Risk[a] (90% CI) |
|---|---|---|---|---|
| | FluMist N=6473 | Placebo N=3216 | | |
| Acute Respiratory Tract Events | 771 | 387 | 83.58/84.23 | 0.99 (0.90, 1.10) |
| Systemic Bacterial Infections | 0 | 0 | 0/0 | NA |
| Acute Gastrointestinal Tract Events | 107 | 65 | 11.60/14.15 | 0.82 (0.63, 1.06) |
| Rare Events Potentially Related to Influenza | 3 | 1 | 0.33/0.22 | 1.49 (0.22, 19.41) |

*Note:* NA, not available, due to 0 events.

[a] Based on participant-incidence.

During the safety evaluation period, 147 MAE diagnostic categories were reported in study participants in any of the utilization settings (hospital, ED, or outpatient clinic) (Appendix 2). Fifteen of the 147 MAE categories were associated with a statistically significant increased relative risk in FluMist recipients in at least one of the binomial analyses (Table 73), and fourteen categories were associated with a statistically significant decreased relative risk in FluMist recipients (Table 74). Two of these categories (abdominal pain and acute gastrointestinal tract events) were associated with both an increased and decreased relative risk in FluMist recipients depending on the utilization setting and age group (Tables 73 and 74).

## Table 73
## MAEs Associated with a Statistically Significant Increased Relative Risk in FluMist Recipients

| MAE(s) | Age | Utilization Setting[a] | Dose[b] | Number of Participants | | Rate per 1000 person-months[c], FluMist/Placebo | Binomial Relative Risk[c] (90% CI) |
|---|---|---|---|---|---|---|---|
| | | | | FluMist n/N | Placebo n/N | | |
| Conjunctivitis | 1–17 Years | Combined | One | 49/6473 | 12/3216 | 6.73/3.32 | 2.03 (1.21, 3.53) |
| | | Clinic | One | 48/6473 | 12/3216 | 6.60/3.32 | 1.99 (1.18, 3.46) |
| | | Combined | Combined | 69/6473 | 21/3216 | 7.48/4.57 | 1.64 (1.09, 2.50) |
| | | Clinic | Combined | 68/6473 | 21/3216 | 7.37/4.57 | 1.61 (1.08, 2.46) |
| | 1–8 Years | Clinic | One | 31/3769 | 8/1868 | 7.80/4.07 | 1.92 (1.02, 3.83) |
| | | Combined | One | 32/3769 | 8/1868 | 8.06/4.07 | 1.98 (1.05, 3.95) |
| | 18–35 Months | Clinic | One | 9/728 | 0/369 | 11.63/0 | NA (1.74, NA) |
| | | Combined | One | 9/728 | 0/369 | 11.63/0 | NA (1.74, NA) |
| | | Clinic | Combined | 17/728 | 3/369 | 14.52/5.17 | 2.81 (1.05, 9.07) |
| | | Combined | Combined | 17/728 | 3/369 | 14.52/5.17 | 2.81 (1.05, 9.07) |
| URI | 1–17 Years | ED | One | 9/6473 | 0/3216 | 1.24/0 | NA (1.70, NA) |
| | 1–8 Years | ED | One | 7/3769 | 0/1868 | 1.76/0 | NA (1.27, NA) |
| Asthma | 18–35 Months | Combined | One | 6/728 | 0/369 | 7.75/0 | NA (1.08, NA) |
| OME | 1–8 Years | Clinic | Two | 21/2080 | 4/1045 | 10.79/4.09 | 2.64 (1.12, 7.13) |
| Acute Respiratory Tract Events | 1–17 Years | ED | One | 31/6473 | 8/3216 | 4.26/2.21 | 1.93 (1.02, 3.85) |
| | 9–17 Years | ED | One[d] | 8/2704 | 0/1348 | 2.42/0 | NA (1.50, NA) |
| Abdominal Pain | 1–17 Years | ED | Combined | 11/6473 | 1/3216 | 1.19/0.22 | 5.48 (1.17, 59.20) |
| Acute Gastrointestinal Tract Events | 9–17 Years | ED | One[d] | 6/2704 | 0/1348 | 1.82/0 | NA (1.07, NA) |
| Musculoskeletal Pain | 1–8 Years | Clinic | One | 20/3769 | 3/1868 | 5.04/1.53 | 3.30 (1.26, 10.54) |
| | | | Combined | 26/3769 | 5/1868 | 4.39/1.70 | 2.59 (1.19, 6.21) |
| | 18–35 Months | Clinic | One | 7/728 | 0/369 | 9.04/0 | NA (1.30, NA) |
| | | | Combined | 7/728 | 0/369 | 5.98/0 | NA (1.27, NA) |
| Cellulitis | 1–8 Years | Clinic | Combined | 31/3769 | 8/1868 | 5.24/2.72 | 1.93 (1.02, 3.85) |
| Benign Lesion | 1–8 Years | Clinic | Combined | 15/3769 | 2/1868 | 2.53/0.68 | 3.73 (1.17, 16.46) |
| Enuresis | 1–17 Years | Clinic | Combined | 13/6473 | 1/3216 | 1.41/0.22 | 6.48 (1.41, 69.15) |
| Speech Delay | 1–17 Years | Clinic | One | 7/6473 | 0/3216 | 0.96/0 | NA (1.28, NA) |
| | 1–8 Years | Clinic | One | 7/3769 | 0/1868 | 1.76/0 | NA (1.27, NA) |
| UTI | 1–17 Years | Clinic | One | 23/6473 | 5/3216 | 3.16/1.38 | 2.29 (1.04, 5.54) |
| | | | Combined | 28/6473 | 7/3216 | 3.04/1.52 | 1.99 (1.01, 4.19) |
| | 9–17 Years | Clinic | One[d] | 13/2704 | 1/1348 | 3.93/0.61 | 6.50 (1.41, 69.36) |
| Seborrhea | 1–17 Years | Clinic | Combined | 6/6473 | 0/3216 | 0.65/0 | NA (1.06, NA) |
| Otitis Externa | 1–8 Years | Clinic | One | 6/3769 | 0/1868 | 1.51/0 | NA (1.06, NA) |

*Note:* NA, not available, due to 0 events occurring in the placebo group.

[a] Analyses were performed separately by setting (Clinic, ED, or Hospital) for all listed MAEs and combined across the three settings (Combined) for conjunctivitis, URI, asthma, acute respiratory tract events, abdominal pain, and acute gastrointestinal tract events.

[b] Analyses were performed separately by dose (Dose One or Dose Two) and combined across doses (Combined).

[c] Based on participant-incidence.

[d] Participants 9–17 years of age received a one dose regimen.

## Table 74
## (1 of 2)
## MAEs Associated with a Statistically Significant Decreased Relative Risk in FluMist Recipients

| MAE(s) | Age | Utilization Setting[a] | Dose[b] | Number of Participants | | Rate per 1000 person-months[c], FluMist/Placebo | Binomial Relative Risk[c] (90% CI) |
|---|---|---|---|---|---|---|---|
| | | | | FluMist n/N | Placebo n/N | | |
| Cough | 1–17 Years | Clinic | Combined | 20/6473 | 19/3216 | 2.17/4.14 | 0.52 (0.31, 0.89) |
| | | Combined | Combined | 20/6473 | 19/3216 | 2.17/4.14 | 0.52 (0.31, 0.89) |
| | 1–8 Years | Clinic | Combined | 15/3769 | 14/1868 | 2.53/4.76 | 0.53 (0.29,0.99) |
| | | Combined | Combined | 15/3769 | 14/1868 | 2.53/4.76 | 0.53 (0.29, 0.99) |
| | | Clinic | Two | 4/2080 | 6/1045 | 2.05/6.14 | 0.33 (0.11, 0.99) |
| | | Combined | Two | 4/2080 | 6/1045 | 2.05/6.14 | 0.33 (0.11, 0.99) |
| Tonsillitis | 1–17 Years | Clinic | Combined | 2/6473 | 6/3216 | 0.22/1.31 | 0.17 (0.03, 0.62) |
| | | Combined | Combined | 2/6473 | 6/3216 | 0.22/1.31 | 0.17 (0.03, 0.62) |
| | | Clinic | One | 1/6473 | 6/3216 | 0.14/1.66 | 0.08 (0.01, 0.43) |
| | | Combined | One | 1/6473 | 6/3216 | 0.14/1.66 | 0.08 (0.01, 0.43) |
| | 1–8 Years | Clinic | Combined | 2/3769 | 6/1868 | 0.34/2.04 | 0.17 (0.03, 0.62) |
| | | Combined | Combined | 2/3769 | 6/1868 | 0.34/2.04 | 0.17 (0.03, 0.62) |
| | | Clinic | One | 1/3769 | 6/1868 | 0.25/3.05 | 0.08 (0.01, 0.43) |
| | | Combined | One | 1/3769 | 6/1868 | 0.25/3.05 | 0.08 (0.01, 0.43) |
| Wheezing | 1–17 Years | Clinic | Combined | 18/6473 | 16/3216 | 1.95/3.48 | 0.56 (0.32, 1.00) |
| Wheezing/SOB | 1–17 Years | Combined | Combined | 19/6473 | 17/3216 | 2.06/3.70 | 0.56 (0.32, 0.97) |
| | | | One | 12/6473 | 12/3216 | 1.65/3.32 | 0.50 (0.25, 0.99) |
| Abdominal Pain | 1–8 Years | Clinic | One | 6/3769 | 9/1868 | 1.51/4.58 | 0.33 (0.13, 0.79) |
| | | Clinic | Combined | 8/3769 | 10/1868 | 1.35/3.40 | 0.40 (0.18, 0.88) |
| | | Combined | One | 8/3769 | 10/1868 | 2.01/5.09 | 0.40 (0.18, 0.88) |
| Acute Gastroenteritis | 12–17 Months | Clinic | One | 0/171 | 3/90 | 0/31.82 | 0 (0, 0.61) |
| | | Combined | One | 0/171 | 3/90 | 0/31.82 | 0 (0, 0.61) |
| Constipation | 9–17 Years | Clinic | One[d] | 1/2704 | 5/1348 | 0.30/3.03 | 0.10 (0.01, 0.55) |
| | | Combined | One[d] | 1/2704 | 5/1348 | 0.30/3.03 | 0.10 (0.01, 0.55) |
| Acute Gastrointestinal Tract Events | 1–17 Years | Combined | One | 81/6473 | 56/3216 | 11.13/15.49 | 0.72 (0.54, 0.96) |
| | | Clinic | One | 74/6473 | 54/3216 | 10.17/14.93 | 0.68 (0.51, 0.92) |
| | 1–8 Years | Combined | One | 48/3769 | 35/1868 | 12.08/17.81 | 0.68 (0.47, 0.98) |
| | | Clinic | One | 45/3769 | 33/1868 | 11.33/16.79 | 0.67 (0.46, 0.99) |
| | 12–17 Months | Combined | One | 0/171 | 4/90 | 0/42.42 | 0 (0, 0.41) |
| | | Clinic | One | 0/171 | 4/90 | 0/42.42 | 0 (0, 0.41) |
| Febrile Illness | 1–17 Years | Clinic | Combined | 6/6473 | 9/3216 | 0.65/1.96 | 0.33 (0.13, 0.80) |
| | 1–8 Years | Clinic | Combined | 5/2870 | 8/1868 | 0.84/2.72 | 0.31 (0.11, 0.80) |
| Viral Syndrome | 1–8 Years | Clinic | Two | 22/2080 | 21/1045 | 11.30/21.48 | 0.53 (0.32, 0.87) |
| | 1–17 Years | Clinic | Combined | 103/6473 | 67/3216 | 11.17/14.58 | 0.77 (0.59, 0.99) |
| Gingivitis | 1–17 Years | Clinic | Combined | 6/6473 | 8/3216 | 0.65/1.74 | 0.37 (0.15, 0.92) |
| | | Clinic | One | 5/6473 | 7/3216 | 0.69/1.94 | 0.35 (0.13, 0.95) |

*Note:* SOB, shortness of breath.

[a] Analyses were performed separately by setting (Clinic, ED, or Hospital) for all listed MAEs and combined across the three settings (Combined) for cough, tonsillitis, wheezing, wheezing/SOB, abdominal pain, acute gastroenteritis, constipation, and acute gastrointestinal tract events.

[b] Analyses were performed separately by dose (Dose One or Dose Two) and combined across doses (Combined).

[c] Based on participant-incidence.

[d] Participants 9–17 years of age received a one dose regimen

**Table 74**
**(2 of 2)**
**MAEs Associated with a Statistically Significant Decreased Relative Risk in FluMist Recipients**

| MAE(s) | Age | Utilization Setting[a] | Dose[b] | Number of Participants | | Rate per 1000 person-months[c], FluMist/Placebo | Binomial Relative Risk[c] (90% CI) |
|---|---|---|---|---|---|---|---|
| | | | | FluMist n/N | Placebo n/N | | |
| Trauma | 1–17 Years | ED | One | 44/6473 | 33/3216 | 6.05/9.13 | 0.66 (0.45, 0.97) |
| | | | Combined | 55/6473 | 42/3216 | 5.96/9.14 | 0.65 (0.47, 0.92) |
| | 1–8 Years | ED | One | 17/3769 | 17/1868 | 4.28/8.65 | 0.49 (0.28, 0.88) |
| | | | Combined | 28/3769 | 26/1868 | 4.73/8.83 | 0.54 (0.34, 0.84) |
| | | Clinic | One | 46/3769 | 35/1868 | 11.58/17.81 | 0.65 (0.45, 0.94) |
| | 12–17 Months | Clinic | Combined | 3/171 | 7/90 | 11.82/52.29 | 0.23 (0.06, 0.70) |
| Vision Disorder | 1–8 Years | Clinic | Two | 15/2080 | 15/1045 | 7.70/15.34 | 0.50 (0.27, 0.92) |
| Well Care/Reassurance/FU | 1–8 Years | ED | One | 4/2870 | 6/1409 | 1.01/3.05 | 0.33 (0.10, 0.98) |

*Note:* FU, follow-up.

[a] Analyses were performed separately by setting (Clinic, ED, or Hospital) for all listed MAEs and combined across the three settings (Combined) for cough, tonsillitis, wheezing, wheezing/SOB, abdominal pain, acute gastroenteritis, constipation, and acute gastrointestinal tract events.

[b] Analyses were performed separately by dose (Dose One or Dose Two) and combined across doses (Combined).

[c] Based on participant-incidence.

### 7.7.6. MAEs Associated With Increased Relative Risk in FluMist Recipients

For some of the MAEs associated with an increased relative risk in FluMist recipients a biologically plausible association with influenza infection could exist. These MAEs are discussed below.

#### 7.7.6.1. Conjunctivitis

Conjunctivitis occurred in 1.1% of FluMist recipients and 0.7% of placebo recipients. Conjunctivitis was associated with a significantly increased relative risk in FluMist recipients in each of the following analyses:

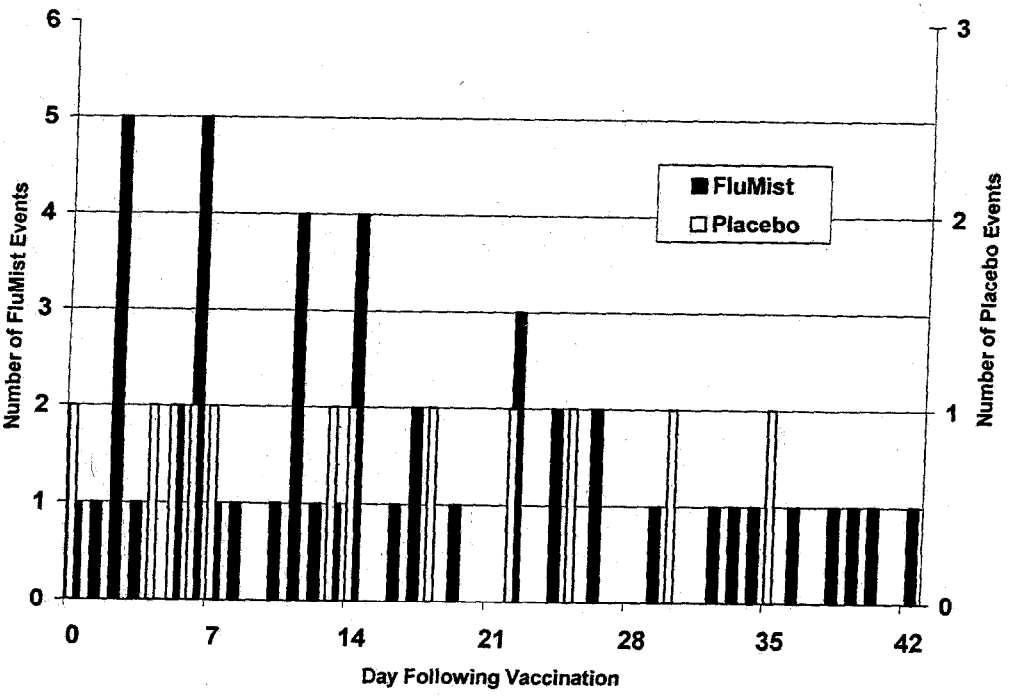
- children 1–17 years of age
  - in the outpatient clinic following Dose One and following all doses combined
  - in all utilization settings combined following Dose One and following all doses combined
- children 1–8 years of age
  - in the outpatient clinic following Dose One

- in all utilization settings combined following Dose One

- children 18–35 months of age
  - in the outpatient clinic following Dose One and following all doses combined
  - in all utilization settings combined following Dose One and following all doses combined

The distribution of conjunctivitis events by day following vaccination after Dose One (for which 88% of expected follow-up was complete) is shown in Figure 15 and appeared to show a clustering of excess events in the FluMist group within the first two weeks following vaccination. Based on this temporal pattern, conjunctivitis appeared to be associated with FluMist administration in the first two weeks following vaccination.

**Figure 15**
**Conjunctivitis Events in the Clinic by Day Following Vaccination for Participants 1–17 Years of Age, after Dose One**




*Note:* Different scale for Y-axes (number of events) used to account for 2:1 randomization ratio.

### 7.7.6.2. Upper Respiratory Infection (URI)

URI occurred in 5.8% of FluMist recipients and 5.8% of placebo recipients. URI was associated with a significantly increased relative risk in FluMist recipients in each of the following analyses:

- children 1 to 17 years of age in the ED following Dose One
- children 1 to 8 years of age in the ED following Dose One

All other analyses of URI, by participant age group, utilization setting, and dose, did not show a statistically significant increased relative risk for FluMist recipients.

The distribution of URI events in FluMist recipients by day following vaccination (days 8, 12, 14, 15, 17, 25, 29, 35, and 41) revealed no apparent clustering or consistent interval of occurrence making the association with vaccination less biologically plausible. Whether or not the increased relative risk for URI in FluMist recipients was related to FluMist administration cannot be definitively determined from these data.

### 7.7.6.3. Asthma

Asthma was recorded in the utilization databases as a MAE in 0.6% of FluMist recipients and 0.7% of placebo recipients. Asthma was only associated with a significantly increased relative risk in FluMist recipients in the following analysis:

- children 18–35 months of age in all utilization settings combined following Dose One

All other analyses of asthma, by participant age group, utilization setting, and dose, did not show a statistically significant increased relative risk for FluMist recipients.

The distribution of asthma events in FluMist recipients by day following vaccination (days 12, 24, 27, 28 [two cases], and 40) revealed no apparent clustering and no consistent interval at which these events occurred. Therefore, the increased relative risk for FluMist recipients appeared unlikely to be related to FluMist administration.

Despite the fact that a history of asthma by parent report was an exclusion for study enrollment, review of the utilization databases and patient records for the six participants in this analysis (Table 73) revealed that four had a diagnosis of asthma prior to trial participation. The two other participants had their initial asthma diagnoses recorded 12 and 40 days following Dose One of FluMist, respectively.

Of note, rates of wheezing and wheezing/shortness of breath were not increased in FluMist recipients in any analysis. In fact, both wheezing and wheezing/shortness of breath were associated with statistically significant decreased relative risks in FluMist recipients 1–17 years of age (Table 74).

#### 7.7.6.4. Otitis Media With Effusion (OME)

OME is a chronic condition not indicative of an acute process.

OME occurred in 0.8% of FluMist recipients and 0.6% of placebo recipients. OME was associated with a significantly increased relative risk for FluMist recipients in the following analysis:

- children 1–8 years of age in the outpatient clinic following Dose Two

Because only 43% of expected follow-up after Dose Two was completed for this interim report, the provisional nature of this result must be considered. Furthermore, because the data following Dose Two were relatively sparse, a temporal relationship between FluMist administration and OME events could not be accurately assessed.

Review of the medical records for participants in this analysis revealed that OME was a preexisting condition at the time of enrollment for 16 of 21 FluMist recipients who had OME recorded following Dose Two. Of the remaining five in the FluMist group, four had multiple prior episodes of acute otitis media.

#### 7.7.6.5. Abdominal Pain

Abdominal pain occurred in 0.5% of FluMist recipients and 0.6% of placebo recipients. Abdominal pain was associated with a significantly increased relative risk in FluMist recipients only in one analysis:

- children 1–17 years of age in the ED following all doses combined

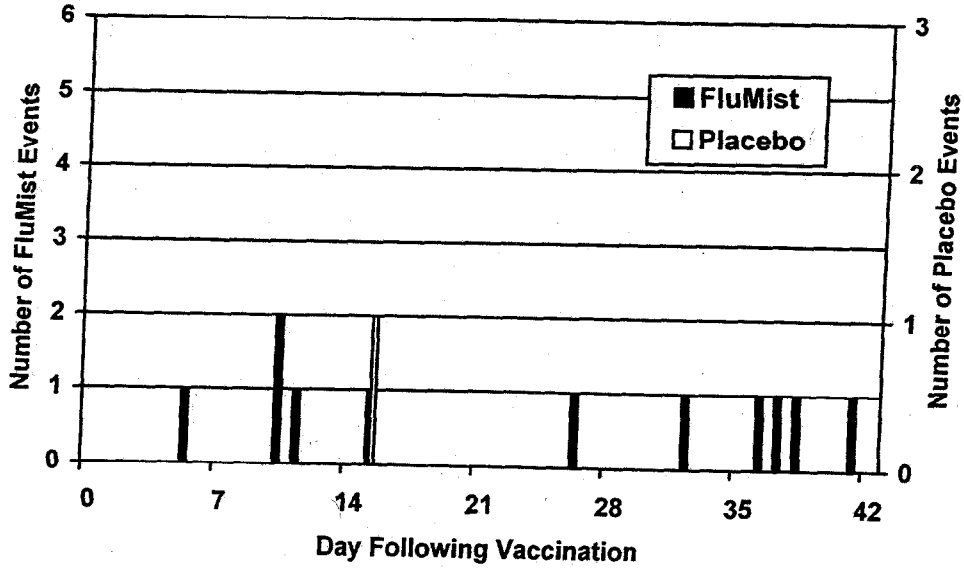
The relative risk for abdominal pain was not increased in the analyses of children 1–8 years of age or 9–17 years of age in any of the utilization settings (ED, outpatient clinic, hospital, or all utilization settings combined), or in the analyses of any age group in any of the utilization settings following Dose One or following Dose Two.

In contrast, the relative risk of abdominal pain was significantly decreased in FluMist recipients 1–8 years of age in all utilization settings combined following Dose One and in the outpatient clinic following Dose One and following all doses combined (Table 74).

In addition, nine separate diagnostic categories that are frequently associated with abdominal pain were analyzed among all participants: appendicitis, gastroenteritis, intestinal obstruction, intussusception, mesenteric adenitis, pancreatitis, perforation, ulcer, and volvulus. Only appendicitis (2 events in FluMist recipients, 1 in placebo) and acute gastroenteritis (47 events in FluMist, 28 in placebo) occurred, and these were proportionately distributed between FluMist and placebo recipients (2:1 randomization). No events were observed in the other diagnostic categories.

The distribution of abdominal pain events by day following vaccination is shown in Figure 16 and demonstrated no apparent clustering and no consistent interval at which these events occurred. The lack of a clear temporal relationship and the variable relative risk increases and decreases seen suggest that the increased relative risk for abdominal pain in FluMist recipients 1–17 years of age was unrelated to FluMist administration.

**Figure 16**
**Abdominal Pain Events in the ED by Day Following Vaccination for Participants 1–17 Years of Age, All Doses Combined**




*Note:* Different scale for Y-axes (number of events) used to account for 2:1 randomization ratio.

### 7.7.6.6. Musculoskeletal Pain

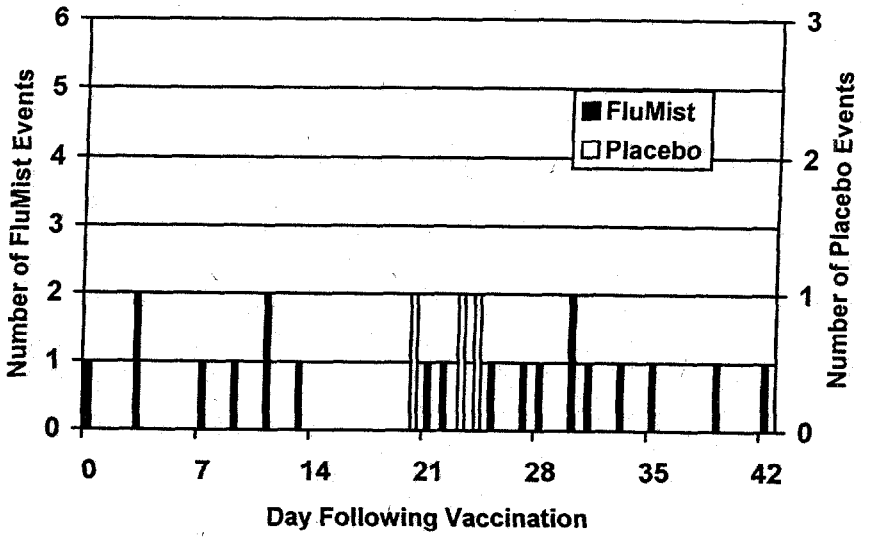
Musculoskeletal pain occurred in 1.4% of FluMist recipients and 1.4% of placebo recipients. Musculoskeletal pain was associated with a significantly increased relative risk in FluMist recipients in the following analyses:

- children 1–8 years in the outpatient clinic following Dose One and following all doses combined
- children 18–35 months of age in the outpatient clinic following Dose One and following all doses combined.

All other analyses of musculoskeletal pain, by participant age group, utilization setting, and dose, did not show a statistically significant increased relative risk for FluMist recipients.

The distribution of the musculoskeletal pain events that occurred in children 1–8 years by day following vaccination for FluMist and placebo recipients is shown in Figure 17 and revealed no consistent interval at which these events occurred, making the association less biologically plausible. Whether or not the increased relative risk for musculoskeletal pain in FluMist recipients was related to FluMist administration cannot be definitively determined from these data.

**Figure 17**
**Musculoskeletal Pain Events in the Clinic by Day Following Vaccination for Participants 1–8 Years of Age, After Dose One**




*Note:* Different scale for Y-axes (number of events) used to account for 2:1 randomization ratio.

### 7.7.6.7. Cellulitis

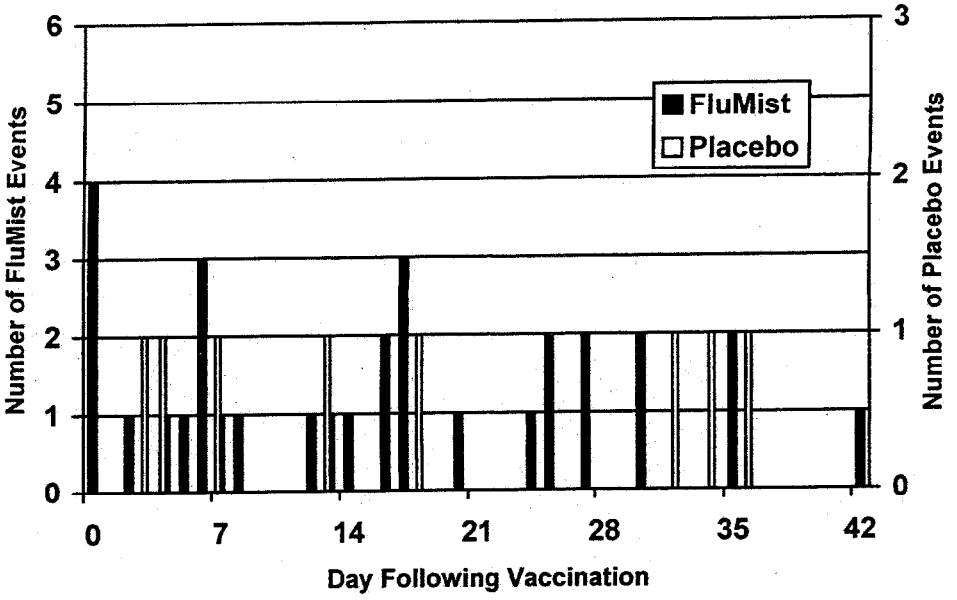
Cellulitis occurred in 0.8% of FluMist recipients and 0.7% of placebo recipients. Cellulitis was associated with a significantly increased relative risk in FluMist recipients only in the following analysis:

- children 1–8 years of age in the outpatient clinic following all doses combined

All other analyses of cellulitis, by participant age group, utilization setting, and dose, did not show a statistically significant increased relative risk for FluMist recipients.

Specific conditions that contributed to the MAE term "cellulitis" were determined by medical record review and included impetigo (n=21), cellulitis/abscess (n=13), balanoposthitis (n=2), paronychia (n=2), and plantar fasciitis (n=1). The distribution of the cellulitis events by day following vaccination is shown in Figure 18. After excluding cellulitis events reported on Day 0 (for which a vaccine relationship was highly improbable) no apparent clustering or consistent interval at which these events occurred was seen. Therefore, the increased relative risk associated with cellulitis in FluMist recipients appeared unrelated to vaccination.

Figure 18
Cellulitis Events in the Clinic by Day Following Vaccination for Participants 1–8 Years of Age, All Doses Combined




*Note:* Different scale for Y-axes (number of events) used to account for 2:1 randomization ratio.

### 7.7.6.8. Other MAEs Associated With Increased Relative Risk in FluMist Recipients

MAEs including benign lesion, enuresis, speech delay, UTI, seborrhea, and otitis externa were each found to be associated with an increased relative risk in FluMist recipients. A biological association between receipt of FluMist and the increased relative risk for these events is unlikely.

### 7.7.7. MAEs Associated with Decreased Relative Risk in FluMist Recipients

Fourteen of the 147 MAE categories reported in study participants were associated with a statistically significant decreased relative risk for FluMist recipients in at least one of the binomial analyses. These MAEs are listed in Table 74 and included cough, tonsillitis, wheezing, wheezing/shortness of breath, abdominal pain, acute gastroenteritis, constipation, acute gastrointestinal tract events, febrile illness, viral syndrome, gingivitis, trauma, vision disorder, and well care/reassurance/follow-up. The decreased relative risk for FluMist recipients in all 14 MAEs could have occurred by chance, however, the decrease in some of the events may have

been associated with protection against wild type influenza and may therefore represent a vaccine-attributable effect.

### 7.7.8. Summary

Based upon the data summarized in this report, in which 6,473 participants 1–17 years of age were vaccinated with FluMist compared with 3,216 placebo recipients:

- SAEs occurred at a low rate in FluMist and placebo recipients (0.2%) and none were vaccine-related.
- Medical utilization was similar for FluMist and placebo recipients.
- A similar number of MAEs were increased or decreased in FluMist recipients.
- The MAEs that were associated with an increased relative risk in FluMist recipients occurred at low rates and were not associated with increased rates of serious illness.
- Analyses across all utilization settings combined showed no significant increase in any of the four pre-specified grouped diagnoses. When events within individual utilization settings were analyzed, acute respiratory tract events were significantly increased in the ED for FluMist recipients, and acute gastrointestinal tract events were significantly increased in the ED and decreased in the clinic for FluMist recipients.
- These interim results further support the conclusion that FluMist is safe and well-tolerated in:
  - Children 1–8 years of age, when administered as a one- or two-dose primary regimen of FluMist.
  - Children and adolescents 9–17 years of age, when administered as a single dose primary regimen of FluMist.

## 7.8. Safety Results by High-Risk Population

An indication for vaccination of high-risk populations is not currently requested; however, available data in populations at high-risk for influenza morbidity (including: children, adolescents, and adults with asthma; HIV-infected children; HIV-infected adults; and adults with COPD), are presented to provide additional information on the safety of FluMist.

### 7.8.1. Safety of FluMist in Participants with Asthma

#### 7.8.1.1. Demographics

The overall demographics of all participants with asthma are presented in Table 75. The demographics for asthma participants with reactogenicity events are presented in Table 76.

One thousand three hundred and thirty-one children, adolescents and adults with asthma, or wheezing illness have received FluMist (Table 75). FluMist recipients with asthma were enrolled in two randomized, placebo-controlled trials (Study AV010, N=24; Study AV009, N=23) and an open label study [Study AV012 Year One, N=531; AV012 Year Two, N=496, AV012 Year Three, N=257]. Across all three Study AV012 years, 1,284 participants with a history of wheezing or asthma received FluMist in a single season, 518 for two seasons and 110 for three seasons. An additional 37 asthmatic participants received placebo (Study AV010, N=24; Study AV009, N=13).

#### 7.8.1.2. Serious Adverse Events

SAEs are discussed in Section 7.3.2.

There were nine SAEs reported in participants with asthma and none were vaccine related. One of the nine SAEs involved the respiratory tract; a case of pneumonia occurred 44 days following vaccination.

## Table 75
## Demographic Characteristics of Participants with Asthma at Initial Vaccination with FluMist or Placebo

| | Overall | | Children 1–8 Years | | Children and Adolescents 9–17 Years | | Adults 18–64 Years | |
|---|---|---|---|---|---|---|---|---|
| | FluMist | Placebo | FluMist | Placebo | FluMist | Placebo | FluMist | Placebo |
| **Characteristic** | N=1331 | N=37 | N=754 | N=0 | N=540 | N=24 | N=37 | N=13 |
| **Age (years)** | | | | | | | | |
| Median | 8.0 | 13.0 | 5.0 | 0.0 | 12.0 | 11.0 | 26.0 | 38.0 |
| Mean | 8.3 | 20.6 | 4.6 | 0.0 | 12.0 | 11.2 | 31.1 | 38.0 |
| 25th percentile | 4 | 10 | 3 | 0.0 | 10 | 10 | 18 | 29 |
| 75th percentile | 11 | 29 | 6 | 0.0 | 14 | 13 | 43 | 46 |
| Range | 1–58 | 9–57 | 1–8 | 0–0 | 9–17 | 9–17 | 18–58 | 25–57 |
| **Gender, n (%)** | | | | | | | | |
| Male | 748 (56.2) | 18 (48.6) | 431 (57.2) | 0 ( 0.0) | 306 (56.7) | 12 (50.0) | 11 (29.7) | 6 (46.2) |
| Female | 582 (43.7) | 19 (51.4) | 322 (42.7) | 0 ( 0.0) | 234 (43.3) | 12 (50.0) | 26 (70.3) | 7 (53.8) |
| Not reported | 1 ( 0.1) | 0 ( 0.0) | 1 ( 0.1) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| **Race/Ethnicity, n (%)** | | | | | | | | |
| White | 968 (72.7) | 28 (75.7) | 529 (70.2) | 0 ( 0.0) | 410 (75.9) | 18 (75.0) | 29 (78.4) | 10 (76.9) |
| Black | 123 ( 9.2) | 2 ( 5.4) | 80 (10.6) | 0 ( 0.0) | 38 ( 7.0) | 2 ( 8.3) | 5 (13.5) | 0 ( 0.0) |
| Hispanic | 153 ( 11.5) | 1 ( 2.7) | 99 (13.1) | 0 ( 0.0) | 52 ( 9.6) | 1 ( 4.2) | 2 ( 5.4) | 0 ( 0.0) |
| Asian | 16 ( 1.2) | 4 (10.8) | 5 ( 0.7) | 0 ( 0.0) | 11 ( 2.0) | 2 ( 8.3) | 0 ( 0.0) | 2 (15.4) |
| Other | 48 ( 3.6) | 2 ( 5.4) | 31 ( 4.1) | 0 ( 0.0) | 16 ( 3.0) | 1 ( 4.2) | 1 ( 2.7) | 1 ( 7.7) |
| Not reported | 23 ( 1.7) | 0 ( 0.0) | 10 ( 1.3) | 0 ( 0.0) | 13 ( 2.4) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |

*Note:* Studies contributing participants to this table are listed by population in Table 47.

**Table 76**
**Demographic Characteristics of Asthmatic Participants with Reactogenicity Event Data**

| Characteristic | AV010 (9–17 years) | | AV009 (18–64 years) | | All Ages | |
|---|---|---|---|---|---|---|
| | FluMist | Placebo | FluMist | Placebo | FluMist | Placebo |
| | N=24 | N=24 | N=23 | N=13 | N=47 | N=37 |
| **Age (years)** | | | | | | |
| Median | 12.0 | 11.0 | 43.0 | 38.0 | 16.0 | 13.0 |
| Mean | 12.5 | 11.2 | 39.1 | 38.0 | 25.5 | 20.6 |
| 25th percentile | 11 | 10 | 26 | 29 | 12 | 10 |
| 75th percentile | 14 | 13 | 49 | 46 | 43 | 29 |
| Range | 10–16 | 9–17 | 21–58 | 25–57 | 10–58 | 9–57 |
| **Gender, n (%)** | | | | | | |
| Male | 14 (58.3) | 12 (50.0) | 9 (39.1) | 6 (46.2) | 23 (48.9) | 18 (48.6) |
| Female | 10 (41.7) | 12 (50.0) | 14 (60.9) | 7 (53.8) | 24 (51.1) | 19 (51.4) |
| **Race/Ethnicity, n (%)** | | | | | | |
| White | 23 (95.8) | 18 (75.0) | 18 (78.3) | 10 (76.9) | 41 (87.2) | 28 (75.7) |
| Black | 0 ( 0.0) | 2 ( 8.3) | 4 (17.4) | 0 ( 0.0) | 4 ( 8.5) | 2 ( 5.4) |
| Hispanic | 1 ( 4.2) | 1 ( 4.2) | 1 ( 4.3) | 0 ( 0.0) | 2 ( 4.3) | 1 ( 2.7) |
| Asian | 0 ( 0.0) | 2 ( 8.3) | 0 ( 0.0) | 2 (15.4) | 0 ( 0.0) | 4 (10.8) |
| Other | 0 ( 0.0) | 1 ( 4.2) | 0 ( 0.0) | 1 ( 7.7) | 0 ( 0.0) | 2 ( 5.4) |

### 7.8.1.3. Reactogenicity in Participants with Asthma

Among asthmatics with reactogenicity events collected, the rates were similar between FluMist (N=47) and placebo recipients (N=36) (Table 77). As seen in healthy FluMist recipients, there was an increase in runny nose (FluMist, 59.6%; placebo, 44.4%). No fevers were reported in FluMist recipients with asthma.

**Table 77**
**Reactogenicity Events (Days 0–7) in Participants with Asthma by Study and Treatment Group**

| | AV010 (9–17 years) | | AV009 (18–64 years) | | All Ages | |
|---|---|---|---|---|---|---|
| **Number of Participants** | **FluMist** | **Placebo** | **FluMist** | **Placebo** | **FluMist** | **Placebo** |
| Vaccinated | 24 | 24 | 23 | 13 | 47 | 37 |
| With Diary Data Available | 24 | 23 | 23 | 13 | 47 | 36 |
| **Event** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Any event | 22 (91.7) | 21 (91.3) | 17 (73.9) | 11 (84.6) | 39 (83.0) | 32 (88.9) |
| Cough | 11 (45.8) | 10 (43.5) | 5 (21.7) | 4 (30.8) | 16 (34.0) | 14 (38.9) |
| Sore throat | 10 (41.7) | 13 (56.5) | 7 (30.4) | 4 (30.8) | 17 (36.2) | 17 (47.2) |
| Runny nose | 18 (75.0) | 13 (56.5) | 10 (43.5) | 3 (23.1) | 28 (59.6) | 16 (44.4) |
| Headache | 11 (45.8) | 9 (39.1) | 7 (30.4) | 7 (53.8) | 18 (38.3) | 16 (44.4) |
| Chills | 4 (16.7) | 3 (13.0) | 4 (17.4) | 1 (7.7) | 8 (17.0) | 4 (11.1) |
| Muscle aches | 5 (20.8) | 8 (34.8) | 7 (30.4) | 1 (7.7) | 12 (25.5) | 9 (25.0) |
| Tiredness/Tired/weak | 8 (33.3) | 10 (43.5) | 9 (39.1) | 2 (15.4) | 17 (36.0) | 12 (33.3) |
| Fever: | | | | | | |
| Temp >100°F | 0 ( 0.0) | 2 ( 8.7) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 2 ( 5.6) |
| Temp >102°F | 0 ( 0.0) | 1 ( 4.3) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 2.8) |
| Temp >104°F | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |

### 7.8.1.4. Other Adverse Events

Adverse events other than reactogenicity events were reported in 23.4% of FluMist recipients (N=47) with asthma compared to 27.0% of placebo recipients (N=37) with asthma (Table 78). The most common events reported were respiratory in nature and included nasal congestion (FluMist, 2/47, 4.3%; placebo, 2/37, 5.4%), asthma (FluMist, 2/47, 4.3%; placebo, 1/37, 2.7%), rhinitis (FluMist, 2/47, 4.3%; placebo, 1/37, 2.7%), and URI (FluMist, 1/47, 2.1%; placebo, 1/37, 2.7%).

**Table 78**
**Adverse Events (Days 0–7) in Participants with Asthma**

| | FluMist N=47 | Placebo N=37 |
|---|---|---|
| **Any Adverse Event, n (%)** | **11 (23.4)** | **10 (27.0)** |
| **Body System** | | |
| Preferred Term | **n (%)** | **n (%)** |
| **Body as a whole** | 3 ( 6.4) | 1 ( 2.7) |
| Allergic reaction | 2 ( 4.3) | 0 ( 0) |
| Pain abdominal | 1 ( 2.1) | 0 ( 0) |
| Pain back | 1 ( 2.1) | 0 ( 0) |
| Pain | 0 ( 0) | 1 ( 2.7) |
| Pain chest | 0 ( 0) | 1 ( 2.7) |
| **Cardiovascular** | 0 ( 0) | 1 ( 2.7) |
| Migraine | 0 ( 0) | 1 ( 2.7) |
| **Digestive** | 3 ( 6.4) | 2 ( 5.4) |
| Vomiting | 2 ( 4.3) | 0 ( 0) |
| Gingivitis | 1 ( 2.1) | 0 ( 0) |
| Nausea | 1 ( 2.1) | 1 ( 2.7) |
| Diarrhea | 0 ( 0) | 1 ( 2.7) |
| **Musculoskeletal** | 0 ( 0) | 1 ( 2.7) |
| Arthralgia | 0 ( 0) | 1 ( 2.7) |
| **Nervous** | 2 ( 4.3) | 1 ( 2.7) |
| Dizziness | 1 ( 2.1) | 1 ( 2.7) |
| Insomnia | 1 ( 2.1) | 0 ( 0) |
| **Respiratory** | 7 (14.9) | 3 ( 8.1) |
| Asthma | 2 ( 4.3) | 1 ( 2.7) |
| Congestion nasal | 2 ( 4.3) | 2 ( 5.4) |
| Rhinitis | 2 ( 4.3) | 1 ( 2.7) |
| Epistaxis | 1 ( 2.1) | 0 ( 0) |
| Sinusitis | 1 ( 2.1) | 0 ( 0) |
| URI | 1 ( 2.1) | 1 ( 2.7) |
| **Skin** | 0 ( 0) | 1 ( 2.7) |
| Urticaria | 0 ( 0) | 1 ( 2.7) |
| **Special senses** | 1 ( 2.1) | 2 ( 5.4) |
| Pain ear | 1 ( 2.1) | 0 ( 0) |
| Conjunctivitis | 0 ( 0) | 2 ( 5.4) |

*Note:* Includes only adverse events occurring in ≥1% of participants.

### 7.8.1.5. Measures of Asthma Stability in Children with Moderate to Severe Asthma

Asthma stability data are available for the 48 children and adolescents, 9–17 years of age (FluMist, N=24; placebo, N=24), with moderate to severe asthma who enrolled in Study AV010. Moderate and severe asthma were defined according to the National Heart Lung and Blood Institute Expert Panel Report II, 1997. Potential participants had to demonstrate a forced

expiratory volume at one second ($FEV_1$) <80% of predicted after having withheld albuterol Metered Dose Inhalers (MDI) for eight hours with reversibility of ≥12% after 2 actuations of albuterol MDI. Twenty-nine of the 40 children enrolled were on inhaled steroids. By design, no participant had a course of oral steroids within a month prior to vaccination.

There was no significant difference between FluMist and placebo recipients in the primary measure of asthma stability, percent change in $FEV_1$ from baseline to post-vaccination, or in any of the other measures of asthma stability (daily asthma scores, night time wakening, peak expiratory flow rates, or use of rescue medication).

Two participants in this study experienced asthma exacerbations, both of whom had received FluMist. One participant who reported an exacerbation three days following vaccination was diagnosed as having sinusitis. The other participant reported an exacerbation two days following vaccination and also reported runny nose and cough as reactogenicity events. In both cases, the exacerbations were controlled by outpatient treatment.

#### 7.8.1.6. Summary

FluMist was safe and well-tolerated in children, adolescents, and adults with asthma. FluMist did not significantly affect asthma stability in 24 children and adolescents with moderate to severe asthma. No vaccine related SAEs were reported in 1,331 evaluable FluMist recipients with asthma.

### 7.8.2. Safety of FluMist in HIV-Infected Children

The safety, tolerability, and vaccine virus shedding of FluMist, as well as laboratory measures of HIV status, were assessed in asymptomatic or mildly symptomatic HIV-infected children (CDC Class N1-2 or A1-2) in Study DMID #99-012 conducted by the NIH (BB-IND-7700).

#### 7.8.2.1. Demographics

The demographics of the HIV-infected children and non-HIV-infected control children are presented in Table 79.

The overall mean age was 4.5 years, and the mean ages of HIV-infected and HIV-negative children were similar (4.7 years versus 4.3 years).

**Table 79**
**Demographic Characteristics of Children by HIV Status in Study DMID #99-012**

| Characteristic | HIV-Infected (N=24) | Non-HIV-Infected (N=25) | Total (N=49) |
|---|---|---|---|
| **Age at Vaccination** | | | |
| Minimum | 1.0 | 1.0 | 1.0 |
| 25th Percentile | 2.4 | 2.8 | 2.7 |
| Median | 5.5 | 4.1 | 4.2 |
| 75th Percentile | 6.2 | 5.8 | 6.1 |
| Maximum | 8.0 | 7.8 | 8.0 |
| Mean (Std. Dev.) | 4.7 (2.2) | 4.3 (1.9) | 4.5 (2.1) |
| **Gender, n (%)** | | | |
| Male | 13 (54) | 15 (60) | 28 (57) |
| Female | 11 (46) | 10 (40) | 21 (43) |
| **Race/Ethnicity, n (%)** | | | |
| Black | 16 (67) | 11 (44) | 27 (55) |
| White | 3 (13) | 5 (20) | 8 (16) |
| Hispanic | 4 (17) | 8 (32) | 12 (24) |
| American Indian or Alaska Native | 0 ( 0) | 1 ( 4) | 1 ( 2) |
| Other | 1 ( 4) | 0 ( 0) | 1 ( 2) |

### 7.8.2.2. Serious Adverse Events

SAEs are discussed in Section 7.3.2.

Three SAEs (one following a dose of placebo and two after a dose of FluMist in a single child) occurred in two HIV-infected children. No SAE was judged to be related to study vaccination. No child was withdrawn from the study because of an AE.

### 7.8.2.3. Reactogenicity in HIV-Infected Children

Rates of fever or other reactogenicity events were not significantly different between HIV-infected and non-HIV-infected children following each FluMist administration, or between FluMist and placebo recipients within each HIV status group. The rates after the second dose of FluMist were generally lower than those observed after the first administration of FluMist.

**Table 80**
**Reactogenicity Events (Day 0 to Day 10) following FluMist One, FluMist Two, or Placebo in Study DMID #99-012**

| | HIV-Infected | | | Non-HIV-Infected | | |
|---|---|---|---|---|---|---|
| **Number of Participants** | **FluMist First Dose** | **FluMist Second Dose** | **Placebo** | **FluMist First Dose** | **FluMist Second Dose** | **Placebo** |
| Vaccinated | 23 | 16 | 24 | 25 | 24 | 25 |
| With Diary Data | 23 | 15 | 24 | 25 | 24 | 25 |
| **Event** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Fever[a] | 1 ( 4) | 1 ( 7) | 2 ( 8) | 3 (12) | 1 ( 4) | 1 ( 4) |
| Runny Nose | 9 (39) | 3 (20) | 5 (21) | 15 (60) | 8 (33) | 14 (56) |
| Sore Throat | 3 (13) | 1 ( 7) | 1 ( 4) | 1 ( 4) | 0 ( 0) | 1 ( 4) |
| Cough | 7 (30) | 3 (20) | 9 (38) | 7 (28) | 4 (17) | 5 (20) |
| Muscle Aches | 0 ( 0) | 0 ( 0) | 1 ( 4) | 0 ( 0) | 0 ( 0) | 0 ( 0) |
| Nausea/Vomiting | 2 ( 9) | 1 ( 7) | 2 ( 8) | 0 ( 0) | 0 ( 0) | 1 ( 4) |
| Headache | 2 ( 9) | 1 ( 7) | 3 (13) | 3 (12) | 0 ( 0) | 1 (4) |
| Irritability | 4 (17) | 0 ( 0) | 3 (13) | 1 ( 4) | 2 ( 8) | 4 (16) |
| Chills | 0 ( 0) | 1 ( 7) | 2 ( 8) | 1 ( 4) | 0 ( 0) | 1 ( 4) |
| Decreased Activity | 3 (13) | 0 ( 0) | 0 ( 0) | 0 ( 0) | 1 ( 4) | 1 ( 4) |
| Itchy or watery eyes | 2 ( 9) | 0 ( 0) | 0 ( 0) | 0 ( 0) | 0 ( 0) | 0 ( 0) |
| Ear Ache | 0 ( 0) | 0 ( 0) | 1 ( 4) | 0 ( 0) | 0 ( 0) | 0 ( 0) |
| **Any of the Above** | **14 (61)** | **5 (33)** | **13 (54)** | **19 (76)** | **9 (38)** | **15 (60)** |

[a] Fever was defined as a temperature >100.4°F oral, rectal or aural or >100°F axillary or missing method.
Study regimens:
Regimen 1 = FluMist, Placebo, FluMist
Regimen 2 = Placebo, FluMist, FluMist

### 7.8.2.4. Shedding of Vaccine Viruses

Seven (28%) of the non-HIV-infected children and three (13%) of the HIV-infected children shed vaccine virus within 10 days of vaccination. No children of either HIV status group had detectable vaccine virus shedding 28–35 days after receipt of vaccine. All recovered influenza isolates were tested for temperature sensitivity and were determined to have retained this phenotype.

### 7.8.2.5. Other Adverse Events

Rates of adverse events after the first dose of FluMist were not significantly different from those observed after placebo within each HIV status group. In general, after the second dose of FluMist, the rates of adverse events were lower for both the non-HIV-infected and HIV-infected children. The rates of adverse events were generally higher in the HIV-infected group compared to the non-HIV-infected group after receipt of both placebo and FluMist. The differences, however, did not achieve statistical significance.

## Table 81
## Summary of Adverse Events by HIV Status and FluMist/Placebo Doses in Study DMID #99-012

| | HIV-Infected | | | Non-HIV-Infected | | |
|---|---|---|---|---|---|---|
| | FluMist One | FluMist Two | Placebo | FluMist One | FluMist Two | Placebo |
| | N=23 | N=16 | N=24 | N=25 | N=24 | N=25 |
| **Any events, n (%)** | 7 (30.4) | 4 (25.0) | 13 (54.2) | 5 (20.0) | 1 (4.2) | 3 (12.0) |
| **Body System** | | | | | | |
| Preferred term | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| **Body as a whole** | **1 ( 4.3)** | **0 ( 0.0)** | **2 ( 8.3)** | **1 ( 4.0)** | **0 (0.0)** | **0 ( 0.0)** |
| Allergic reaction | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 4.0) | 0 (0.0) | 0 ( 0.0) |
| Breath holding spell | 1 ( 4.3) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 0 (0.0) | 0 ( 0.0) |
| Fever | 0 ( 0.0) | 0 ( 0.0) | 1 ( 4.2) | 0 ( 0.0) | 0 (0.0) | 0 ( 0.0) |
| Pain abdominal | 0 ( 0.0) | 0 ( 0.0) | 1 ( 4.2) | 0 ( 0.0) | 0 (0.0) | 0 ( 0.0) |
| **Digestive** | **1 ( 4.3)** | **0 ( 0.0)** | **2 ( 8.3)** | **0 ( 0.0)** | **0 (0.0)** | **0 ( 0.0)** |
| Anorexia | 1 ( 4.3) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 0 (0.0) | 0 ( 0.0) |
| Diarrhea | 0 ( 0.0) | 0 ( 0.0) | 1 ( 4.2) | 0 ( 0.0) | 0 (0.0) | 0 ( 0.0) |
| Vomiting | 0 ( 0.0) | 0 ( 0.0) | 2 ( 8.3) | 0 ( 0.0) | 0 (0.0) | 0 ( 0.0) |
| **Hemic and Lymphatic** | **0 ( 0.0)** | **1 ( 6.3)** | **1 ( 4.2)** | **0 ( 0.0)** | **0 (0.0)** | **0 ( 0.0)** |
| Enlarged Tonsils | 0 ( 0.0) | 1 ( 6.3) | 0 ( 0.0) | 0 ( 0.0) | 0 (0.0) | 0 ( 0.0) |
| Lymphadenopathy | 0 ( 0.0) | 0 ( 0.0) | 1 ( 4.2) | 0 ( 0.0) | 0 (0.0) | 0 ( 0.0) |
| **Respiratory** | **5 (21.7)** | **3 (18.8)** | **6 (25.0)** | **3 (12.0)** | **1 (4.2)** | **2 ( 8.0)** |
| Asthma | 0 ( 0.0) | 1 ( 6.3) | 1 ( 4.2) | 0 ( 0.0) | 0 (0.0) | 0 ( 0.0) |
| Congestion nasal | 1 ( 4.3) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 4.0) | 0 (0.0) | 1 ( 4.0) |
| Cough | 1 ( 4.3) | 1 ( 6.3) | 3 (12.5) | 0 ( 0.0) | 0 (0.0) | 0 ( 0.0) |
| Infection viral | 2 ( 8.7) | 1 ( 6.3) | 1 ( 4.2) | 1 ( 4.0) | 0 (0.0) | 0 ( 0.0) |
| Pharyngitis | 0 ( 0.0) | 1 ( 6.3) | 0 ( 0.0) | 0 ( 0.0) | 1 (4.2) | 0 ( 0.0) |
| Rhinitis | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 4.0) | 0 (0.0) | 1 ( 4.0) |
| Runny nose | 1 ( 4.3) | 0 ( 0.0) | 2 ( 8.3) | 0 ( 0.0) | 0 (0.0) | 0 ( 0.0) |
| Sinusitis | 1 ( 4.3) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 0 (0.0) | 0 ( 0.0) |
| **Skin** | **1 ( 4.3)** | **1 ( 6.3)** | **5 (20.8)** | **1 ( 4.0)** | **0 (0.0)** | **0 ( 0.0)** |
| Infection | 0 ( 0.0) | 1 ( 6.3) | 2 ( 8.3) | 0 ( 0.0) | 0 (0.0) | 0 ( 0.0) |
| Infection fungal | 0 ( 0.0) | 0 ( 0.0) | 1 ( 4.2) | 0 ( 0.0) | 0 (0.0) | 0 ( 0.0) |
| Rash | 1 ( 4.3) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 4.0) | 0 (0.0) | 0 ( 0.0) |
| Skin disorder | 0 ( 0.0) | 0 ( 0.0) | 2 ( 8.3) | 0 ( 0.0) | 0 (0.0) | 0 ( 0.0) |
| **Special senses** | **2 ( 8.7)** | **0 ( 0.0)** | **2 ( 8.3)** | **1 ( 4.0)** | **0 (0.0)** | **1 ( 4.0)** |
| Ear infection, undifferentiated | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 0 (0.0) | 1 ( 4.0) |
| Otitis media | 2 ( 8.7) | 0 ( 0.0) | 2 ( 8.3) | 1 ( 4.0) | 0 (0.0) | 0 ( 0.0) |

Excludes adverse events with onset greater than 35 days after the preceding vaccination. Includes only adverse events occurring in ≥1% of participants.
Study regimens: 1 = FluMist, Placebo, FluMist, 2 = Placebo, FluMist, FluMist.

### 7.8.2.6. Lack of HIV Disease Progression

No statistically significant differences occurred from baseline to post-vaccination in CD4 counts, CD4% or in HIV viral load in the HIV-infected participants.

### 7.8.3. Safety of FluMist in HIV-Infected Adults

The safety, tolerability, and vaccine virus shedding of FluMist, as well as laboratory measures of HIV status, were assessed in asymptomatic or mildly symptomatic HIV-infected adults (CDC Class A1–2) in Study DMID #98-005 conducted by the NIH (BB-IND-7700).

### 7.8.3.1. Demographics

The demographics of the HIV-infected adults and non-HIV-infected control adults are presented in Table 82.

A total of 57 HIV-infected individuals, 20–58 years of age received FluMist or placebo (Table 82). Initial enrollment included HIV-infected participants with CD4 counts >400 cells/mm$^3$ (9 FluMist, 8 placebo) followed by enrollment of a larger number of HIV-infected participants with CD4 counts >200 cells/mm$^3$ (19 FluMist, 21 placebo). This study enrolled predominantly Black participants, but this was not by design.

**Table 82**
**Demographic Characteristics of Adults by HIV Status in Study DMID #99-005**

| | HIV-Infected Adults | | Non-HIV-Infected Adults | |
|---|---|---|---|---|
| Characteristic | FluMist N=28 | Placebo N=29 | FluMist N=27 | Placebo N=27 |
| **Age (years)** | | | | |
| Median | 40.0 | 40.0 | 38.0 | 27.0 |
| Mean | 40.6 | 39.6 | 36.1 | 30.8 |
| Range | 27–52 | 20–58 | 18–50 | 18–54 |
| 25$^{th}$ percentile | 35 | 34 | 23 | 24 |
| 75$^{th}$ percentile | 47 | 46 | 46 | 40 |
| **Sex, n (%)** | | | | |
| Female | 20 (71.4) | 9 (31.0) | 18 (66.7) | 17 (63.0) |
| Male | 8 (28.6) | 20 (69.0) | 9 (33.3) | 10 (37.0) |
| **Race/Ethnicity, n (%)** | | | | |
| Asian | 0 ( 0.0) | 0 ( 0.0) | 1 ( 3.7) | 1 ( 3.7) |
| Black | 22 (78.6) | 20 (69.0) | 4 (14.8) | 8 (29.6) |
| Hispanic | 0 ( 0.0) | 2 ( 6.9) | 1 ( 3.7) | 1 ( 3.7) |
| Other | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |
| White | 6 (21.4) | 7 (24.1) | 21 (77.8) | 17 (63.0) |

### 7.8.3.2. Serious Adverse Events

SAEs are discussed in Section 7.3.2. One SAE was reported in placebo recipients in the trial; the SAE was considered unrelated to vaccination.

### 7.8.3.3. Reactogenicity in HIV-Infected Adults

As in healthy participants, an increase in runny nose/nasal congestion was seen in FluMist recipients (60.7%) compared to placebo recipients (31.0%) (Table 83).

**Table 83**
**Reactogenicity Events (Days 0–10) in HIV-Infected and HIV-Negative Adults by Treatment Group**

| | HIV-Infected | | HIV-Negative | |
|---|---|---|---|---|
| **Number of Participants** | **FluMist** | **Placebo** | **FluMist** | **Placebo** |
| Vaccinated | 28 | 29 | 27 | 27 |
| With Diary Data Available | 28 | 29 | 27 | 27 |
| **Event** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Any event | 22 (78.6) | 18 (62.1) | 22 (81.5) | 19 (70.4) |
| General Discomfort | 7 (25.0) | 7 (24.1) | 7 (25.9) | 7 (25.9) |
| Runny nose/Nasal congestion | 17 (60.7) | 9 (31.0) | 21 (77.8) | 12 (44.4) |
| Sore Throat | 7 (25.0) | 2 ( 6.9) | 6 (22.2) | 6 (22.2) |
| Cough | 11 (39.3) | 8 (27.6) | 3 (11.1) | 7 (25.9) |
| Muscle aches | 10 (35.7) | 6 (20.7) | 4 (14.8) | 6 (22.2) |
| Nausea/Vomiting | 4 (14.3) | 5 (17.2) | 1 ( 3.7) | 3 (11.1) |
| Decreased appetite | 3 (10.7) | 3 (10.3) | 3 (11.1) | 5 (18.5) |
| Abdominal pain | 2 ( 7.1) | 1 ( 3.4) | 1 ( 3.7) | 3 (11.1) |
| Headache | 11 (39.3) | 9 (31.0) | 12 (44.4) | 11 (40.7) |
| Fever: | | | | |
| Temp 1: Oral >100°F | 2 ( 7.1) | 3 (10.3) | 0 ( 0.0) | 3 (11.1) |
| Temp 2: Oral >102°F | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) |

### 7.8.3.4. Other Adverse Events

Four HIV-infected participants, one placebo and three FluMist recipients, reported other adverse events during the 10 days following vaccination. The placebo recipient reported wheezing and the FluMist recipients reported rash, wheezing, and sinusitis.

### 7.8.3.5. Lack of HIV Disease Progression

There were no statistically significant differences between FluMist and placebo recipients in changes from baseline to post-vaccination assessments in CD4 counts or in HIV viral load as

measured by plasma PCR. One HIV-infected FluMist recipient shed vaccine virus (type B) on Day 5, but not thereafter.

### 7.8.4. Safety in Adults with COPD

Neither administration of FluMist to patients with COPD nor co-administration of FluMist with Trivalent Inactivated Vaccine (TIV) are being proposed for licensure in the current application. However, to further define the safety of FluMist co-administered with TIV, 2,215 participants with COPD were enrolled in the VA Study CSP #448. The demographic data and SAEs from this trial are reviewed.

#### 7.8.4.1. Demographics

The demographics of this population are presented in Table 49. Concurrently with TIV, 1,107 adults with COPD received FluMist and 1,108 received placebo mist. There were no demographic differences between FluMist and placebo recipients. The mean and median ages were approximately 68 years. Ninety-eight percent of participants were male and most were white.

#### 7.8.4.2. Serious Adverse Events

SAEs are discussed in Section 7.3.2. Six hundred nine SAEs were reported in this study of patients with COPD; 31 were considered vaccine related (9 FluMist recipients, 22 placebo recipients).

### 7.8.5. Safety in Adults ≥65 Years of Age

The demographics of this population are presented in Table 49. The mean and median years of age is approximately 70 and approximately one third are female.

#### 7.8.5.1. Serious Adverse Events

SAEs are discussed in Section 7.3.2. Four serious adverse events were reported; two after receipt of FluMist and two after receipt of placebo. No SAEs were vaccine related.

#### 7.8.5.2. Reactogenicity in Adults ≥65 Years of Age

Overall, 45.0% of FluMist recipients compared to 39.6% of placebo recipients reported any reactogenicity event (Table 84). The proportion in the two treatment groups reporting any specific reactogenicity event was similar, except for sore throat (FluMist, 13.5%; placebo, 2%). Nine of the 15 (60%) FluMist recipients with sore throat experienced sore throat for two days or less.

**Table 84**
**Reactogenicity Events (Days 0–7) in Adults ≥65 Years of Age by Treatment Group**

| Number of Participants | FluMist | Placebo |
|---|---|---|
| Vaccinated | 111 | 101 |
| With Diary Data Available | 111 | 101 |
| **Event** | **n (%)** | **n (%)** |
| Any event | 50 (45.0) | 40 (39.6) |
| Cough | 10 ( 9.0) | 9 ( 8.9) |
| Sore throat | 15 (13.5) | 2 ( 2.0) |
| Runny nose | 31 (27.9) | 24 (23.8) |
| Headache | 17 (15.3) | 15 (14.9) |
| Chills | 5 ( 4.5) | 7 ( 6.9) |
| Muscle aches | 15 (13.5) | 14 (13.9) |
| Tiredness | 20 (20.0) | 16 (16.0) |
| Fever: | | |
| Temp 1: >100°F, oral | 3 ( 2.7) | 1 ( 1.0) |
| Temp 2: >102°F, oral | 1 ( 0.9) | 0 ( 0.0) |
| Temp 3: >104°F, oral | 0 ( 0.0) | 0 ( 0.0) |

### 7.8.5.3. Other Adverse Events

Adverse events were uncommon in adults ≥65 years of age (Table 85). The most common AE in both groups was rhinitis (FluMist, 8.1%; placebo, 4.0%).

**Table 85**
**Adverse Events (Days 0–7) in Adults ≥65 Years of Age**

| | FluMist | Placebo |
|---|---|---|
| | N=111 | N=101 |
| **Any Event, n (%)** | **21 (18.9)** | **16 (15.8)** |
| **Body System** | | |
| Preferred Term | **n (%)** | **n (%)** |
| **Body as a whole** | 2 ( 1.8) | 5 ( 5.0) |
| Pain | 0 ( 0.0) | 3 ( 3.0) |
| **Digestive** | 3 ( 2.7) | 4 ( 4.0) |
| Nausea | 2 ( 1.8) | 2 ( 2.0) |
| Diarrhea | 1 ( 0.9) | 2 ( 2.0) |
| **Respiratory** | 14 (12.6) | 7 ( 6.9) |
| Rhinitis | 9 ( 8.1) | 4 ( 4.0) |
| Lung disorder | 0 ( 0.0) | 2 ( 2.0) |
| **Special senses** | 3 ( 2.7) | 2 ( 2.0) |
| Conjunctivitis | 2 ( 1.8) | 2 ( 2.0) |

*Note:* Includes only adverse events occurring in ≥1% of participants.

#### 7.8.5.4. Summary

FluMist was safe and well-tolerated in adults ≥65 years of age, most of whom had an additional chronic condition associated with high risk for influenza related morbidity and mortality other than age. FluMist was associated with a 11% increase in sore throat versus placebo. Co-administration of FluMist with TIV did not increase the rate of injection site reactions.

### 7.9. Other Safety Information

#### 7.9.1. Drug/Vaccine Interactions

There is no safety information to report regarding possible interactions between FluMist and any drug or other vaccines. Study AV018 has been initiated to assess concomitant use of FluMist with MMRII® and VARIVAX® vaccines in children 12–15 months of age. Of the 1,200 children planned, 160 have been enrolled.

#### 7.9.2. Overdose, Abuse or Misuse

There is no safety information to report regarding overdosing, abuse or misuse of FluMist.

#### 7.9.3. Safety of FluMist in Pregnant Women

Thirteen pregnancies have been reported in FluMist trials (10 FluMist and three placebo recipients). Nine participants were vaccinated after their last menstrual period (10 to 51 days) and three prior to their last menstrual period (23–96 days). In the other pregnancy, the date of the last menstrual period was not estimated.

Eight of the 13 pregnancies, seven in FluMist recipients and one in a placebo recipient, resulted in delivery of healthy infants. Three pregnancies (one FluMist and two placebo recipients) ended in spontaneous abortion. Another pregnancy in a FluMist recipient ended with a therapeutic abortion. One pregnancy in a FluMist recipient resulted in the delivery of a pre-term infant (estimated 37 week gestation).

#### 7.9.4. Effects of Long-Term Exposure

A total of 12,846 children, regardless of health status, 1 to 8 years of age received 22,618 doses of FluMist (Table 47). Two or more doses were administered to 6,995 children, three or more doses were administered to 1,629 children, and four or more doses were administered to 677 children. Of the total of 12,846 children 1–8 years of age, 12,069 were healthy children.

A total of 6,861 children and adolescents, regardless of health status, 9–17 years of age received 9,404 doses of FluMist (Table 47). Two or more doses were administered to 1,796

children and adolescents and 737 received three or more doses. Of the total of 6,861 children 9–17 years of age, 6,321 were healthy children.

Four thousand seven hundred and seventy-one children and adolescents 1–17 years of age were re-vaccinated for a second annual season; 1,999 were re-vaccinated for a third season and 549 children were re-vaccinated for a fourth season.

FluMist was safe and well-tolerated with repeat administration over additional influenza seasons in children 1–8 years of age and in children 9–17 years of age.

### 7.9.5. *Transmission*

Assessment of transmission of vaccine virus is important to the safety evaluation of a live virus vaccine. The transmissibility of monovalent and bivalent formulations of CAIV has been examined in healthy children and young adults in studies conducted prior to the development of FluMist. In ten published studies in which close contacts of monovalent and bivalent CAIV recipients were monitored, there was no reported evidence of transmission.

At the November 1998 VRBPAC meeting, Dr. Peter Wright of Vanderbilt University presented unpublished data that 2 of 40 placebo recipients shed vaccine virus after exposure to more than 100 vaccine recipients. More than 80% of the vaccinees shed vaccine. Dr. Wright also stated that these two children did not have a seroresponse to influenza.

Data has recently become available from a double-blind, placebo-controlled study to evaluate transmission in children in daycare. The trial was conducted by Wyeth-Lederle Vaccines (Study D145-P500) in Finland. The primary objective of the study was to assess whether FluMist is transmitted from vaccinated children to their unvaccinated contacts in a daycare setting which may be conducive to transmission. Transmissibility was to be evaluated in terms of the proportion of placebo recipients from whom any of the vaccine strains were isolated.

One hundred ninety-seven children ≥8 months and <36 months of age who attended day care were randomized 1:1 to receive a single dose of FluMist or placebo. Table 86 presents the baseline demographic information for the study population. Ninety-eight received a first dose of FluMist, while 99 received a first dose of placebo.

**Table 86**
**Demographic Characteristics of the Population in Study D145-P500**

| Characteristic | FluMist N=98 | Placebo N=99 |
|---|---|---|
| **Age at Dose One (months)** | | |
| Median (Standard Deviation) | 27.0 ( 6.7) | 25.8 ( 6.7) |
| Mean | 28.6 | 27.1 |
| Range (Min. – Max.) | (10.0 – 35.8) | (9.2 – 36.0) |
| **Gender, n (%)** | | |
| Male | 44 (45) | 44 (44) |
| Female | 54 (55) | 55 (56) |
| **Race/Ethnicity, n (%)** | | |
| White | 95 (97) | 96 (97) |
| Black | 2 ( 2) | 1 ( 1) |
| Asian | 1 ( 1) | 0 ( 0) |
| Other | 0 ( 0) | 2 ( 2) |

Nasal swab samples were cultured for influenza virus three times per week for 21 days after administration of the first dose of vaccine or placebo. Eighty percent of vaccine recipients shed at least one of the three FluMist strains.

One placebo recipient shed Type B vaccine virus on a single day, 15 days after enrollment in the study. The placebo recipient had symptoms similar to that reported by the majority of participants in the study, regardless of treatment group. The shed virus was temperature sensitive and cold adapted. Therefore, one case of transmission of FluMist occurred. The shedding rate was 1.75% with an upper bound of the 95% confidence interval of 8%.

### 7.10. Safety Summary

In the combined population of children, adolescents and adults enrolled in clinical studies of FluMist, those adverse events occurring at least 5% more frequently in the FluMist recipients than placebo recipients were runny nose and/or nasal congestion and sore throat. Events were transient with a peak incidence on Day Two post-vaccination and generally lasted for less than three days.

In children (1–8 years of age), the adverse event occurring at least 5% more frequently in FluMist recipients than placebo recipients following a first dose of FluMist was runny nose and/or nasal congestion (58% versus 48%).

In healthy adults (18–64 years of age), the adverse events occurring at least 5% more frequently in FluMist recipients than placebo recipients were runny nose (44% versus 27%) and sore throat (26% versus 17%).

Rates of common adverse events in older adults (65–81 years of age), children and adults with asthma, and HIV-infected children and HIV-infected adults receiving FluMist were similar to those in healthy children and healthy adults. In older adults, only sore throat was reported significantly more often than in the placebo group (14% versus 2%).

### 7.11. Safety Conclusions

Based upon the data from clinical studies, the following conclusions can be made:

- FluMist has been safe and well-tolerated in the following healthy populations:
  - Children 1–8 years of age, when administered as a one- or two-dose primary regimen.
  - Children 1–8 years of age, when administered for annual re-vaccination during three additional consecutive years.
  - Children and adolescents 9–17 years of age, when administered as a single primary regimen.
  - Children and adolescents 9–17 years of age when administered for annual re-vaccination during two additional consecutive years.
  - Healthy adults 18–64 years of age, when administered as a single primary regimen.
- FluMist appears to be safe and well-tolerated in limited numbers of participants in the following high-risk populations:
  - Children and adolescents 9–17 years of age with moderate to severe asthma, when administered as a single primary regimen.
  - Asymptomatic or mildly symptomatic HIV-infected children who are in CDC class N1-2 or A1-2 when administered as a two-dose primary regimen.
  - Asymptomatic or mildly symptomatic HIV-infected adults who are in CDC Class A1-2 (CD4 ≥200 cells/mm3, without AIDS-defining illness), when administered as a single primary regimen.

- High-risk adults with COPD or adults ≥65 years of age when administered concurrently with TIV.

- The small increase in post-vaccination reactogenicity events and low risk of other adverse events are acceptable given the benefits of influenza prevention.
- Vaccine related SAEs in healthy populations 1–64 years of age are rare.
- FluMist may be transmitted from vaccinees to unvaccinated contacts at a low frequency in a daycare setting.